The New England
Journal of Medicine

Copyright, 1949, by the Massachusetts Medical Society

Volume 241 NOVEMBER 3, 1949 Number 18

PULMONARY EMBOLISM*

A Statistical Study of Post-Mortem Material at the Massachusetts General Hospital

BENSON B. ROE, M.D.,† AND JOEL C. GOLDTHWAIT, M.D.‡

BOSTON

CONSIDERABLE interest has been manifested in the subject of thromboembolism during the past few years, and numerous reports have appeared in the literature on the various preventive measures. As far as we know, however, no long-range mortality statistics following an extended trial of one method of treatment have been reported, and it is our purpose here to analyze the possible effects of femoral-vein interruption on the mortality of pulmonary embolism at the Massachusetts General Hospital.

Interruption of the femoral veins was introduced in this hospital in 1939 as a measure hoped to be of value in the prevention of fatal pulmonary embolism. The procedure was employed in selected cases during the four-year period from 1939 to 1942, and the results[1] from this small group were sufficiently encouraging that a large-scale program was undertaken in the attempt to obliterate or to reduce the mortality from this distressing complication. Special attention was given to the problem, and more careful vigilance for the manifestations of pulmonary infarction and thrombophlebitis in the deep leg veins was maintained on both general surgical services and later to a large extent throughout the hospital. Bilateral interruptions of the femoral veins were done in large numbers for minimal indications and later (see Table 1) on an even greater scale with the addition of prophylactic interruptions in older age groups. Earlier reports[2-6] have attempted evaluation of this immense effort from a clinical standpoint. It is the purpose of this paper merely to report the autopsy statistics for the five-year period 1943 through 1947, during which 1929 bilateral femoral-vein interruptions were done, as compared with similar earlier periods before the advent of specific preventive measures. Our two control series are taken prior to 1941, and the period between 1941 and 1943 is omitted because vein interruptions were done on such a small scale as to have no significant effect on the whole hospital mortality rate.

The material for this study was obtained from the autopsy protocols from 1930 through 1947 and from the hospital records of patients. No case that did not come to autopsy was used, and every case with the autopsy finding of pulmonary embolism was reviewed. Classification of the data was difficult and necessarily arbitrary, but similar criteria were used in the comparative series. We were impressed with the large personal element in evaluating the records and protocols, as well as the variability of details within them, and, therefore, must urge caution in the use of these figures in comparison with other series.

TABLE 1. *Incidence of Therapeutic and Prophylactic Femoral-Vein Interruption in 1929 Cases at the Massachusetts General Hospital.*[6]

YEAR	THERAPEUTIC OPERATIONS	PROPHYLACTIC OPERATIONS	TOTALS
1943	150	15	165
1944	208	72	280
1945	214	178	392
1946	259	289	548
1947	227	317	544
Totals	1,058	871	1,929

To eliminate the cases of doubtful significance and the question of incomplete autopsy dissection, we have listed separately all cases in which the embolus or emboli were small and improbable as the cause of death. The remaining cases of fatal embolism were further divided into two groups: the first with massive emboli unquestionably lethal, and the second with large emboli considered to be of fatal magnitude (labeled: "Large ? Fatal") but open to some challenge as the actual cause of death because of an atypical terminal clinical course or the presence of other fatal disease of equal or greater magnitude.

*From the Department of Pathology and Bacteriology, Massachusetts General Hospital.

†Assistant resident surgeon, Massachusetts General Hospital.

‡Assistant resident in medicine, Veterans Administration Hospital, West Roxbury; formerly, assistant resident in pathology, Massachusetts General Hospital.

The findings of the three five-year periods — 1931 through 1935, 1936 through 1940 and 1943 through 1947 — are tabulated below. The total number of autopsies in each period was about the same, and it seems reasonable to assume that these are equally representative major samples of total deaths. The sharp increment of small emboli from 2.2 per cent in the first period to 5.4 per cent in the second, as pointed out in the third column of Table 2, is undoubtedly attributable to the focus of attention in the pathology laboratory on this problem and consequent emphasis on more complete routine dissection of the pulmonary vascular tree. It is our impression, however, that these figures are still unreliable because of the variability of this routine and the difficulty of standardizing the pathologist's interpretation. For this reason we have included under "small" all emboli described as lodging in secondary or smaller branches of the pulmonary artery even though some of them were extensive enough to suggest at least a precipitating cause of death. The ones considered to be probably or definitely fatal were described as organized clots lying in and occluding no less than two primary branches of the right or left pulmonary artery so as to block a major portion of the pulmonary circulation. Subdivision of the large emboli as described above was more or less arbitrary but where there was any reasonable doubt they were listed under "Large ? Fatal." It is interesting that these disputable cases remained very constant between the three periods and probably are a source of less inaccuracy than we feared. The massive emboli, and hence the totals, showed a steady and appreciable increase, which was exactly the same (2.7 to 3.5 per cent) in the recent period as that between the first and second control periods (1.9 to 2.7 per cent), as shown in the fourth column of Table 2.

The steady increase of deaths from pulmonary embolism in spite of venous interruptions can perhaps be explained on the basis of the relative decline of other diseases and complications with the advent of chemotherapy, blood banks, improved technics and so forth, as well as the rising number of older patients in the hospital census. In addition, it has been suggested that the increasing number of cancer patients and the greater magnitude of surgery are responsible for this increase although it is notable that thromboembolism appears through a wide range of age, primary disease, and operative procedure (see Tables 5, 6 and 7). Statistical evaluation of these changing factors is impractical if not impossible, and we can but recognize their influence on the net result.

Further to analyze the comparative statistics between the preligation era and the recent series, we were obliged to introduce corrective factors as much as possible. It must be taken into account that during the recent period of venous interruptions the procedure was considered but not done in many cases in which advanced incurable malignant lesions seemed to contraindicate strenuous preventive measures. We therefore separated these cases from both series (see Table 3) to arrive at a figure of deaths from pulmonary embolism that

TABLE 2. *Incidence of Pulmonary Embolism in Total Autopsies (Massachusetts General Hospital).*

DATE	NO. OF AUTOPSIES	CASES WITH SMALL, INCIDENTAL EMBOLI		CASES WITH FATAL EMBOLI					
				MASSIVE		LARGE ?FATAL		TOTAL	
		no.	*percentage*	*no.*	*percentage*	*no.*	*percentage*	*no.*	*percentage*
1931 1935	1,991	43	2.16	37	1.86	15	0.75	52	2.16
1936 1940	1,832	99	5.40	49	2.67	18	0.98	67	3.66
1943 1947	2,083	111	5.33	73	3.50	19	0.91	92	4.42

TABLE 3. *Analysis of Deaths from Pulmonary Embolism.*

PERIOD	TOTAL ADMISSIONS	TOTAL AUTOPSIES	TOTAL DEATHS FROM PULMONARY EMBOLISM		CASES OF ADVANCED INCURABLE CANCER		DEATHS THAT SHOULD HAVE BEEN PREVENTED	
			MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM	MASSIVE FATAL EMBOLISM	LARGE ?FATAL EMBOLISM
1931–1935	67,038	1,991	37	15	3	2	34	13
1936–1940	78,065	1,832	49	18	5	1	44	17
1943–1947	79,951	2,083	73	19	13	4	60	15

it would be desirable to prevent. This figure in the last series, however, can further be challenged as not representing the failures of the whole program of venous interruption since the doctrines of such a program could hardly receive universal acceptance in an institution of this size. It is pointed out that deaths from pulmonary embolism occurred in patients on private services and specialty services who had indications for venous interruption under the precepts of the more vigorous policy. It was therefore necessary to review all the clinical records in the cases of fatal embolism and separate from the previous figure the cases in which, in retrospect, there had been signs suggestive of warning pulmonary infarction or venous thrombosis in the legs according to the criteria used by the peripheral vascular service.* We were also obliged to rule out the autopsies on patients whose embolic episode occurred outside the hospital, where early diagnosis may have been overlooked and prompt venous interruption was impossible. The remaining number of deaths from pulmonary embolism after the "corrections" represents the failures of the over-all program, assuming it to have been properly executed throughout the hospital.

It is evident, then, that all the autopsy percentages fall within the same range, and the lower figure of 2.54 per cent for the recent period is not significantly smaller than the preceding one.

It must be pointed out that these figures demonstrate not only the effect of so-called "therapeutic" venous interruption on thromboembolic mortality but also the sum total effect of all preventive measures exercised. Early ambulation, prophylactic interruptions and anticoagulants unquestionably play an important role, but they obviously cannot be separately evaluated from this material. However, since there had been no significant change in the mortality figures in the presence of all factors, it seems reasonable to assume that there would have been no significant change had these factors acted singly. Not only has the total figure for this period been unchanged but figures for individual years† have remained surprisingly constant despite the recent — during the past two years — increased use of prophylactic interruptions and anticoagulants.‡

It has not been our purpose to evaluate so-called "prophylactic" venous interruption but as a corollary to Table 3 it is interesting to point out that of the 53 total net deaths in the last period 14 fell into the category that, in retrospect, would have received prophylactic interruption according to the proponents of this more recent measure.§ Application of this figure to the above data has not been made and would hardly be judicious except in the most theoretical sense because of the narrower scope of the procedure, but if one accepted this added correction, as well as the assumption that venous interruption would prevent all emboli, the net total deaths would be reduced from 53 to 39, which would drop the incidence to a significantly lower figure: 1.87 per cent.

Fatal Pulmonary Emboli Following Femoral-Vein Interruption

In the course of this study a group of patients was collected in the recent five-year period who had received bilateral femoral-vein interruption, either superficial or common, and who also had an anatomic diagnosis of pulmonary embolism at autopsy. This group was included in the above series, but we believe that further analysis of these cases is warranted. The group included a total of 26 cases. Of these, 16 were discarded for the following reasons: in 1 case the emboli were composed of tumor from a renal-cell carcinoma; in 6 cases the emboli were considered small enough to be incidental as a cause of death; in 5 cases the embolus might have been the immediate cause of death, but was not classified as such because of its size

Table 3 (*Continued*).

Cases without Venous Interruption but with Indications in Retrospect		Cases with Onset of Signs Outside Hospital		Net Deaths			Percentage of Autopsies	Percentage of Admissions
Massive Fatal Embolism	Large ?Fatal Embolism	Massive Fatal Embolism	Large ?Fatal Embolism	Massive Fatal Embolism	Large ?Fatal Embolism	Totals		
—	—	—	—	34	13	47	2.36 (±0.34*)	0.07
—	—	—	—	44	17	61	3.33 (±0.42*)	0.08
11	2	7	2	42	11	53	2.54 (±0.34*)	0.07

*Calculated standard error of percentage.

*Bilateral interruptions of the superficial femoral veins were done as an emergency procedure on any patient with otherwise unexplained signs of deep-calf or popliteal tenderness; measurable calf or ankle swelling; localized pulmonary consolidation by x-ray study unless interpretation could rule out infarct; sudden chest pain or hemoptysis or both (even with negative x-ray examination); and, in many cases, when simultaneous rise of temperature, pulse and respiration was accompanied by minimal or equivocal evidence of one or more of the above.

†Total deaths from thromboembolism by years were: 1943, 15; 1944, 25; 1945, 12; 1946, 15; and 1947, 25.

‡In all, over 800 patients received Dicumarol in some dosage through 1947.

§Prophylactic bilateral interruptions of the superficial femoral veins were done on patients over sixty years of age preceding or within forty-eight hours of a major surgical procedure and in certain younger patients such as those with peritonitis who were to be immobilized in Fowler's position.

or the importance of other diseases (uremia, peritonitis and so forth); and in 4 cases the clinical course suggested that massive embolism had occurred prior to the venous interruption. The remaining 10 cases in which there was a clear-cut picture of massive fatal pulmonary embolism following venous interruption are discussed in Table 4.

It is apparent that there is nothing remarkable about the age and sex distribution in these cases; all but 2 patients were over sixty years of age. The primary disease seemed to represent a fair random sample of that found in the whole group of fatal pulmonary emboli. It is of interest, but of doubtful significance, that the group contained no cases of congestive heart failure. The fatal embolism in Case 3, which followed an eye operation, suggested that the operative procedure itself was probably of little significance.

Five patients in this group had venous interruptions for prophylactic reasons, but one of these cases was later reclassified under therapeutic (see footnote in Table 4); 3 were done after a warning pulmonary infarct, and 2 because of thrombophlebitis in the deep venous system of the legs. Clots were found in the veins at operation only in the last 2 cases. In the 4 cases classified as prophylactic

TABLE 4. *Data in Clear-Cut Cases of Massive Fatal Embolism following Femoral-Vein Interruption.*

PATIENT	AGE	PRIMARY DISEASE	REASON FOR INTERRUPTION	CLOTS FOUND AT OPERATION	INTERVAL FROM INTERRUPTION TO DEATH	SOURCE OF FATAL EMBOLUS
	yr.					
M. McD.	75	Thrombophlebitis, deep veins of legs	Leg signs	Yes	11 days	Unknown (restricted autopsy)
C. S.	74	Carcinoma of colon with metastases	Pulmonary infarct 3 days after peritoneoscopy	No	8 days	Left deep femoral vein occluded at junction of middle and lower thirds
C. B.	70	Cataracts	Pulmonary infarct 3 days after eye operation	No	2 days	Thrombi in left common femoral, internal and common iliac and right common iliac veins
L. B.	62	Incisional hernia in scar of hysterectomy; obesity.	Prophylactic interruption 2 days after hernia repair	No	13 days	"Currant-jelly clot" in 3-cm. stump of superficial femoral on left; attached to this, 8 cm. of red-gray laminated thrombus in common femoral vein; otherwise clear.
E. M.	74	Diabetes mellitus; gangrene of toes.	Prophylactic interruption 2 days after low thigh amputation*	No	2 days	Thrombus in 1-cm. stump of right superficial femoral vein continuous with 7-cm. clot in common femoral vein; otherwise clear.
W. D.	42	Subarachnoid hemorrhage	Interruption on 2nd hospital day because of calf tenderness	Yes (right side only)	13 days	Right common femoral vein ligated; this and iliac vessels thrombosed to mouth of vena cava; left side clear.
J. P.	78	Arteriosclerotic gangrene of foot	Prophylactic interruption at time of low thigh amputation	No	2 hr.	No thrombus found in common femoral veins or deep femoral veins 8 cm. below sites of operation
G. C.	68	Carcinoma of colon	Prophylactic interruption on 5th hospital day 5 days after cecostomy	No	17 days (8 days after resection)	Iliac common and deep femoral veins clear as far as examined—8 cm. below operative sites
E. B.	77	Thrombophlebitis with pulmonary infarct 1 day prior to admission.	Pulmonary infarct; interruption on day of admission.	No	13 days	Thrombosis of left external iliac common and deep femoral veins; thrombus 0.5 cm. in diameter at ligation site on right.
D. S.	54	Carcinoma of stomach	Prophylactic interruption 2 days after total gastrectomy	No	32 days	Thrombi 2 cm. long extending into common femoral vein from each interruption site

*Because at autopsy the clot in the common femoral vein was considered to be several days old and thus probably antedating interruption, the procedure was classified as "inadequate therapy" in retrospect.

TABLE 5. *Incidence of Fatal Pulmonary Emboli by Age Groups.*

AGE	1931–1935			1936–1940			1943–1947		
	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS	MASSIVE FATAL EMBOLI	LARGE ?FATAL EMBOLI	TOTALS
yr.									
0–19	0	1	1	0	0	0	0	0	0
20–29	0	2	2	1	1	2	1	1	2
30–39	2	1	3	4	0	4	2	1	3
40–49	6	1	7	5	1	6	8	4	12
50–59	9	1	10	12	4	16	16	3	19
60–69	8	6	14	9	9	18	22	3	25
70–79	10	2	12	16	3	19	18	6	24
80–89	2	1	3	2	0	2	5	1	6
90–99	0	0	0	0	0	0	1	0	1
Totals	37	15	52	49	18	67	73	19	92

interruptions, 1 patient was found at autopsy to have a blind stump of the superficial femoral vein in which a clot had developed and propagated into the common femoral vein. One patient had both superficial femoral veins tied flush with no pouches, and yet thrombi were found adherent to the ligation site on both sides. The other 2 patients had no clots demonstrated in the leg veins.

These 10 patients represent a mortality rate of 0.5 per cent in the over-all program of 1929 bilateral femoral-vein interruptions. The 4 prophylactic interruptions in this group represent a 0.5 per cent mortality among the 871 prophylactic interruptions done during that period.

Table 6. *Distribution of Fatal Pulmonary Emboli according to Primary Disease.*

Primary Disease	1931–1935		1936–1940		1943–1947	
	Massive Fatal Emboli	Large ?Fatal Emboli	Massive Fatal Emboli	Large ?Fatal Emboli	Massive Fatal Emboli	Large ?Fatal Emboli
Gastrointestinal tract and biliary system:						
Benign	12	1	3	0	4	2
Malignant	4	1	5	2	14	1
Malignant with metastases	1	0	4	1	10	1
Gynecologic system:						
Benign	2	0	4	0	4	0
Malignant	0	0	0	0	3	0
Malignant with metastases	1	2	1	0	0	1
Genitourinary system:						
B nign	9	1	4	2	2	0
Malignant	3	1	6	1	1	0
Malignant with metastases	0	0	0	0	1	1
Chest:						
Benign	1	0	0	0	5	2
Malignant	0	0	0	0	3	0
Hernias	0	0	2	0	2	0
Breast lesions	1	1	0	1	2	0
Cardiovascular disease	1	5	4	6	6	6
Peripheral vascular disease	1	0	1	1	3	2
Thrombophlebitis	0	0	3	0	1	1
Miscellaneous (neurosurgical, orthopedic and eye conditions and so forth)	1	3	12	4	12	2
Totals	37	15	49	18	73	19

Table 7. *Distribution of Fatal Pulmonary Emboli according to Operation.*

Operation	1931–1935		1936–1940		1943–1947	
	Massive Fatal Emboli	Large ?Fatal Emboli	Massive Fatal Emboli	Large ?Fatal Emboli	Massive Fatal Emboli	Large ?Fatal Emboli
Exploratory laparotomy	4	2	4	0	5	0
Resection or exteriorization of gastrointestinal tract	6	1	7	2	20	1
Appendectomy or drainage of appendiceal abscess	1	1	0	0	2	0
Cholecystectomy	5	0	2	0	2	0
Herniorrhaphy	0	0	2	0	2	0
Procedures on uterus and ovaries	1	0	4	0	4	0
Procedures on kidneys, adrenal glands and ureters	2	0	3	0	1	0
Procedures on bladder and prostate	9	1	8	2	3	0
Exploratory thoracotomy	0	0	0	0	3	0
Empyema drainage	1	0	0	0	0	0
Transthoracic procedure	0	0	0	0	(3*)	0
Amputation	1	0	1	0	2	0
Mastectomy	1	1	0	1	1	0
Miscellaneous (neurosurgical, orthopedic and eye procedures and so forth)	1	0	5	0	10	3
Peritoneoscopy	0	0	0	0	1	0
	0	0	0	0	7	0
Totals	32	6	36	5	64	4

*These were all operations on the esophagus or stomach and are included under the heading "Resection or Exteriorization of Gastrointestinal Tract."

Fatal Pulmonary Embolism without Warning

It is of interest that a breakdown of the 92 deaths from pulmonary embolism in the recent five-year period reveals that 49 or 53 per cent occurred without any clinical warning whatsoever (that is, no signs of pulmonary infarct or thrombophlebitis). In some cases, of course, the record makes no specific reference to signs that may have gone unnoticed (it should be pointed out again, however, that the entire house staff was aware of the problem during this period, and most of the records contained periodic notes about leg and chest examinations). Of the remaining 43 patients 25, or

27 per cent, were known to have had one or more warnings, either in the legs or by pulmonary infarct, but the records on the ante-mortem course of the other 18 cases are incomplete or absent.

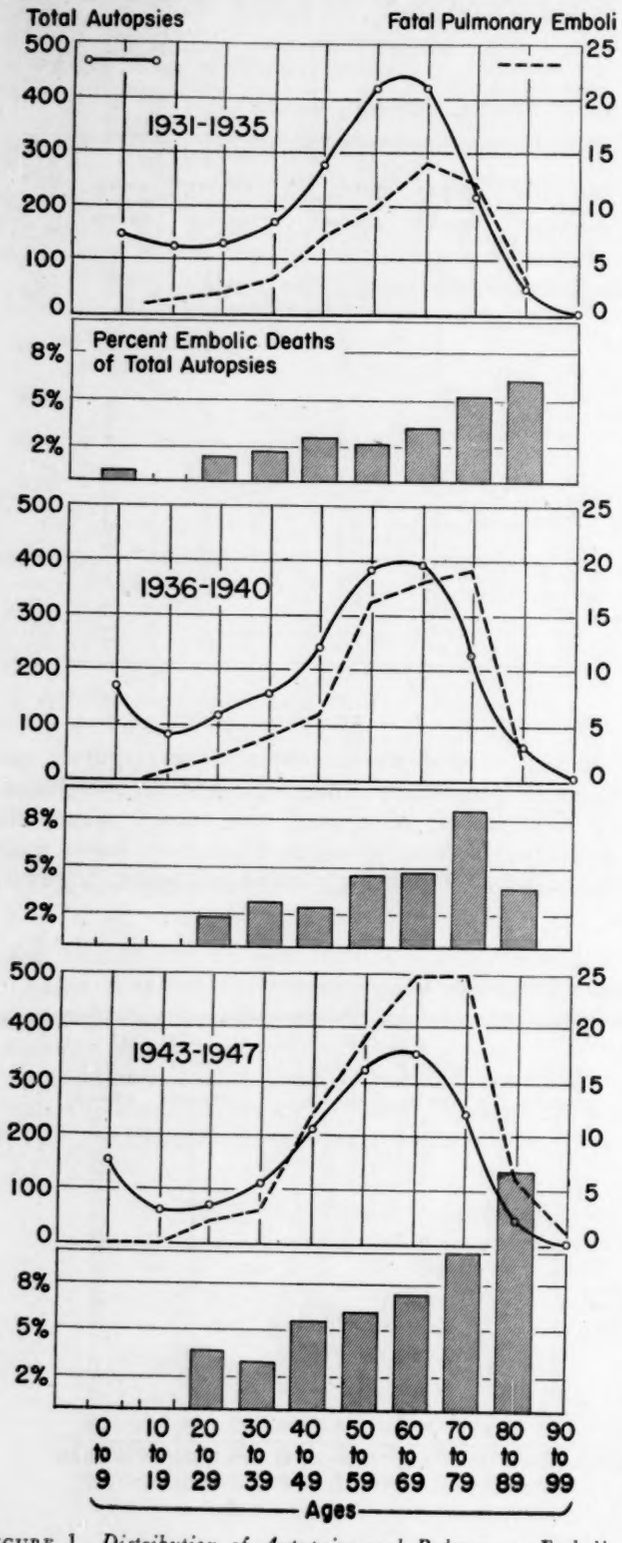

FIGURE 1. *Distribution of Autopsies and Pulmonary Emboli by Age Groups.*

This figure of unheralded fatal emboli is somewhat higher than that given in other reports. DeTakats[7] states that one fifth to one fourth of emboli are fatal at first occurrence, and Evans and Dee,[8] of the Lahey Clinic, reported premonitory signs in 85 per cent of their fatal cases. One can only speculate over this discrepancy. Perhaps its cause is the successful surgical treament of patients with warning infarcts or thrombophlebitis. However, there is apparently considerable variation in the criteria used for "warning," and this should be considered seriously as the principal cause. We did not believe that a review of the hospital records in the period before venous interruption would provide a suitable comparison because so little attention was focused on the problem that the signs were probably more often missed than recorded.

DISTRIBUTION OF FATAL EMBOLISM

Table 5, 6 and 7 are presented as supplementary information gathered during the course of this study and do not have any direct bearing on the more pertinent over-all figures. However, the distribution of fatal pulmonary embolism is of considerable interest, and although our figures in each group are too small for individual analysis the material may prove useful in the compilation of more extensive data.

Age

That pulmonary embolism is a disease more common in the older age groups is demonstrated in Table 5. It is significant, however, that approximately 20 per cent of all fatal emboli occurred in ages below fifty, in which total deaths were less numerous. Thus, if the ratio of deaths from pulmonary embolism is plotted in relation to total deaths, or autopsies (Fig. 1), there is a more slowly rising curve, which supports the initial statement but which also emphasizes the wide age distribution of the disease.

It is interesting that comparison between these curves for the different periods studied shows no dramatic shift that could be interpreted as an effect of preventive measures. In fact, if anything, there is a shift toward the higher age groups in the recent period despite concentration of preventive efforts on this group. This is probably due to the constant increase in the average age of patients admitted (a sample study from 1930 and 1943 [thirteen years] showed an increase of eight years).

Primary Disease

The deaths from pulmonary embolism have been further analyzed in Table 6 and 7 with regard to the primary disease and operative procedure with which they were associated.

It should be made clear that comparison between any two figures in these tables cannot be considered valid since there is no statistically significant difference between them according to sample statistical analysis. However, Table 6 shows that massive fatal pulmonary embolism occurs in a

wide variety of diseases and that although a few are found in medical conditions, the majority of emboli complicate surgical disease and occur during the postoperative period. Comparison of the totals in Table 6 and 7 demonstrates this fact.

The decline of pulmonary embolism as a complication of benign conditions of the gastrointestinal and biliary tracts is more apparent than real, being exaggerated by a combination of many different types of disease under one heading. The same reservation can be made for benign conditions of the genitourinary system, although in both these categories it is undoubtedly true that operative procedures are not so formidable and convalescence not so prolonged as they were fifteen years ago. The increasing number of patients with pulmonary embolism complicating malignant lesions of the gastrointestinal and biliary systems is probably a reflection of the increased number of patients with cancer in the hospital population. We have not analyzed this in more detail because, considering the questionable significance of the figures as they stand, nothing would be contributed by such a study.

Also of interest is the fact that diseases in which the treatment has been fairly standardized for many years (uterine fibroids, hernias and lesions of the breast) show an apparently constant incidence of embolism.

It should be noted that the absence of fracture cases in this list is due to the fact that all such deaths came under the jurisdiction of the medical examiner and do not appear in our autopsy files.

Operative Procedure

In similar fashion it is seen that fatal pulmonary emboli follow a wide variety of operative procedures. The chief point to be made in Table 7 is the fairly constant number of deaths from pulmonary emboli with the different procedures throughout the three periods. The increased number of fatal emboli following gastrointestinal-tract resection is probably accounted for by the increased number of patients in the hospital population subjected to operation for gastrointestinal cancer. The decrease following operations on the bladder and prostate has been attributed to femoral-vein interruption.[9]

In Table 5, 6 and 7 the obvious question arises over what these figures represent in terms of ratio to total hospital population by age group, total patients treated in each disease category and total operations performed in each category. These data, however, were not readily available and are essentially beyond the scope of this paper, which is an analysis of autopsy figures only.

Discussion

In an evaluation of this study it becomes evident that the incidence of pulmonary embolism is affected by a complex interplay of factors. The introduction of femoral-vein interruption is only one of many considerations, and the impossibility of evaluating separately the other factors makes it equally impossible to evaluate the effect of one method in terms of the sum total.

It can be said, however, that a five-year, large-scale program of femoral-vein interruption has failed to alter significantly the mortality figures for pulmonary embolism as compared with earlier, similar periods.

The problem is further confused by the introduction of conflicting factors, which have tended to increase the incidence of thromboembolism during the same period of preventive efforts. Some of these are technical and therapeutic advances that have reduced other fatal complications and kept sick patients alive for a longer period in which to develop venous thrombi; an increasing number of geriatric patients, in whom pulmonary embolism is more common; an increasing proportion of cancer patients in this hospital, also with a somewhat higher incidence; and more heroic surgical procedures from which convalescence is often prolonged and complicated. The extent to which these factors have actually promoted thromboembolic disease cannot be accurately determined*; however, if their effect has been appreciable it might be postulated that a higher expected mortality rate has been kept down by the preventive program. It is regrettable that our controls had to be taken from a virtually different era rather than a comparable set of circumstances, but no group sufficiently large for comparison was deprived of some preventive measure.

Mortality statistics alone are not a satisfactory criterion for evaluating a procedure, and it should be pointed out that clinical analysis of selected patients demonstrates more favorable results from femoral-vein interruption in preventing fatal pulmonary embolism. The continued high incidence of the disease at the autopsy table, however, suggests that the problem remains unsolved.

Summary

At the completion of a five-year program of femoral-vein interruption, autopsy statistics of pulmonary embolism are reviewed for this period and compared with those for two previous five-year periods.

These figures are analyzed and corrected in an attempt to demonstrate more accurately the effect of the program.

Analysis is made of the pulmonary embolic deaths that followed femoral-vein interruption.

Data are presented on the distribution of fatal emboli by age group, primary disease and operative procedure.

*To demonstrate the magnitude of these changes a sample analysis was made from reports of the general surgical service for the contrasting two-year periods, 1930-31 and 1946-47. In brief it was found that the average age at death has risen from 49.3 to 57.6 years; surgical admissions for malignant lesions have risen from 28 to 44 per cent, whereas admissions for inflammatory disease have decreased relatively from 28 to 14 per cent; and sepsis as a fatal complication on surgical patients has declined from 63 to 37 per cent (of all deaths).

No significant improvement in the mortality figures for pulmonary embolism in the hospital as a whole could be demonstrated in the period of venous interruption.

Because of the many considerations that defied statistical analysis and the inadequacy of control data, no conclusions can be drawn either to support or to negate the value of the program.

References

1. Welch, C. E., and Faxon, H. H. Thrombophlebitis and pulmonary embolism. *J. A. M. A.* **117**:1502-1508, 1941.
2. Allen, A. W., Linton, R. R., and Donaldson, G. A. Thrombosis and embolism: review of 202 patients treated by femoral vein interruption. *Ann. Surg.* **118**:728-740, 1943.
3. *Idem.* Venous thrombosis and pulmonary embolism: further experience with thrombectomy and femoral vein interruption. *J. A. M. A.* **128**:397-403, 1945.
4. Allen, A. W. Thrombosis and embolism: preliminary report on comparative results of femoral vein interruption and dicumarol therapy. *Bull. New York Acad. Med.* **22**:169-184, 1946.
5. Allen, A. W., Linton, R. R., and Donaldson, G. A. Venous thrombosis and pulmonary embolism. *J. A. M. A.* **133**:1268-1276, 1947.
6. Donaldson, G. A. Therapy and prophylaxis of venous thrombosis and pulmonary embolism. *S. Clin. North America* **27**:1037-1051, 1947.
7. DeTakats, G., and Fowler, E. F. Problem of thromboembolism. *Surgery* **17**:153-177, 1945.
8. Evans, J. A., and Dee, J. F. Anticoagulant treatment of postoperative venous thrombosis and pulmonary embolism. *New Eng. J. Med.* **238**:1-5, 1948.
9. Colby, F. H. Venous thrombosis and pulmonary emboli in urology. *J. Urol.* **56**:124-129, 1946.

PLASTIC OPERATION ON THE FALLOPIAN TUBE

Francis M. Ingersoll, M.D.*

BOSTON

During the past fifteen years there has been an increasing interest in the problem of sterility. One of the more difficult obstacles in this field has been occlusion of the oviducts. Rubin's[1] establishment of a diagnostic method for determining tubal patency enabled gynecologists to make a diagnosis of occlusion while hysterosalpingography accurately localized the point of obstruction. From 1932 to 1936 Solomons,[2, 3] Bonney[4] and Holden and Sovak[5] presented encouraging reports concerning operative relief of sterility due to occluded tubes. As Solomons put it, "an occasional good golf shot impels the worst player to persist with the game, so occasional successes impel me and others to try further." However, enthusiasm for the tubal plastics lessened since results were poor, and some authors even discouraged further attempts.

Recently those interested in the problem have stated that even though only 5 to 10 per cent of these women become pregnant postoperatively, an operation is well worth while, after conservative therapy by repeated carbon dioxide insufflation, heat by diathermy or Elliot bag or estrogenic hormone stimulation has been tried. The discovery of nonpatent tubes during a sterility study on many of my own patients stimulated me to look up the results obtained by operative procedures. Twenty-three patients were operated upon at the Massachusetts General and Palmer Memorial hospitals during the years 1932-1947, either on the ward service or in the private practices of Dr. Joe V. Meigs or Dr. Langdon Parsons or myself. Of these, 5 had uterotubal implantations for bilateral cornual obstruction, after which 3 had a normal pregnancy and delivery. Eighteen patients had salpingostomies for occlusion of the fimbriated ends of the tubes, and in these cases no pregnancies have occurred.

The first tubal implantation was performed and recorded by Watkins[6] in 1896, and the patient had a subsequent pregnancy and miscarriage. In 1921 Shaw[7] described a successful tubal implantation performed by Cullen. Solomons[3] reported 6 pregnancies following this procedure. Holden and Sovak[5] discussed 3 cases of tubal implantation with 1 subsequent normal pregnancy, and Sovak[8] later reported another of their cases in which an ectopic pregnancy occurred with rupture of the tube. The accepted technic employed has been a division of the tubes at the point of occlusion, after which patency of the remainder of the tube is demonstrated by air and saline solution injection. The occluded cornual portion is reamed out with a special instrument or by sharp dissection. The patent tube is then pulled into the uterus and held there by stitches (Fig. 1). Patency is again proved by air or water insufflation from the fimbriated end. The serious complications following this operation include exacerbation of pelvic inflammatory disease, and there is the possibility of uterine rupture during pregnancy at the site of implantation of the tube.

The first salpingostomy was reported by Martin[9] in 1885. Nine years later Mackenrodt[10] described the first 2 successful cases. The largest series in the literature is that of Solomons,[3] who in 1936 reported on 366 tubal operations — cornual, isthmic and fimbrial. Two tubal and 28 normal pregnancies occurred — that is, pregnancy was obtained in 8.2 per cent. Bonney reported 70 cases, with follow-up study in 37, in which 7, or 18 per cent, of patients conceived. The results of these operations have varied from 100 cases without a pregnancy[11] to 8 full-term pregnancies after 7 operations.[12]

*Instructor in gynecology, Harvard Medical School; assistant in surgery, Massachusetts General Hospital.

The technic of salpingostomy generally recommended is that of Holden and Sovak[5] — a modification of the circumcision operation devised by Bonney (Fig. 2).[4] The advantage of this operation is that bringing the mucosa back to the serosa for a distance of 1.5 to 2.5 cm. closes the raw edge, and the chances of adhesions and secondary closure are thereby lessened. The technic is as follows: the tube is handled without instruments, and the fimbriated end is opened if possible by gentle, blunt dissection — or a small section of the dilated tube is resected. Patency is tested for with a glass syringe. A urethral catheter, No. 5 Fr., or a piece of polyethene tubing, is threaded into the tube and a Bonney clamp applied to the tube 1.5 to 2.5 cm. from the amputated end. A circular incision is made through the serosa and muscularis at the end of the Bonney clamp. Then, with two fine Allis clamps, the amputated end of the tube is gently pulled backward while the Bonney clamp is slowly

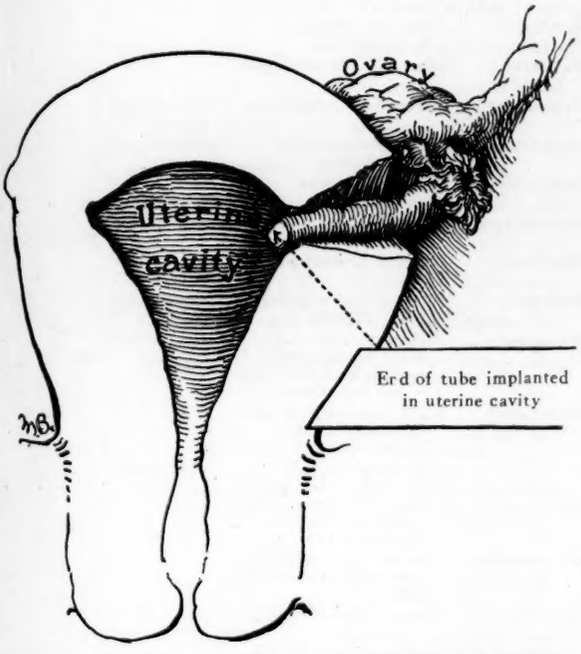

FIGURE 1. *Implantation of the Outer End of the Fallopian Tube into the Uterine Cavity. (Reproduced from Shaw,[7] with the Permission of the Publisher.)*

pushed forward. The tubal cuff so formed is held in place with fine catgut. Tubal patency is again established by the use of the syringe. The tube and ovary are then suspended by a stitch through the hilus of the ovary attached to the pelvic peritoneum. In the 18 salpingostomies reported here a simpler procedure of amputating the end of the hydrosalpinx and then suturing the mucosa to the serosa was employed. None of these patients became pregnant, although in 33 per cent of cases tubal patency was proved by the Rubin test or hysterosalpingography postoperatively. The small diameter of the tube, the friable, infected tissue and the tendency to bleed make it difficult to maintain an adequate lumen.

The serious complication after this operation has been an exacerbation of pelvic inflammatory disease. This occurred once in the 18 cases discussed here. If pregnancy results, abortion sometimes occurs, and ectopic pregnancies have been reported. However, successful pregnancies do occur, and the risks are too slight to contraindicate the operation.

In the patients who had tubal operation three different pathologic conditions seemed to be concerned: infection involving the endosalpinx, such as gonorrhea or tuberculosis; infections spreading through lymphatics and into the muscularis, such as that after septic abortion; and infections around the tube — that is, perisalpingitis similar to that after a ruptured appendix.

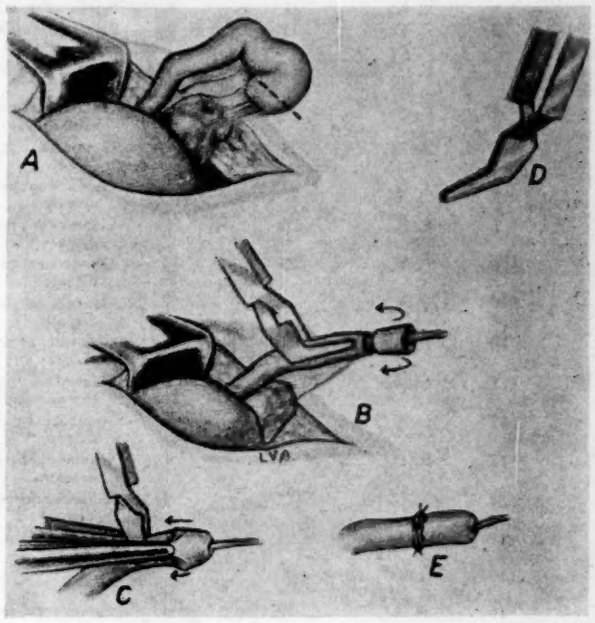

FIGURE 2. *Technic of Salpingostomy. (Reproduced from Siegler,[13] with the Permission of the Publisher.)*

In the 3 patients who became pregnant the infection was limited to the cornual segment of the tube. Success followed implantation because the diseased portion was easily resected. For example, in Case 1 the infection started as endometritis occurring after abortion. At operation it was found that bilaterally only 2.5 cm. of tube near the uterus was scarred and completely blocked. The remainder of the tube seemed to be of normal size, and the fimbriated ends were entirely free. In Case 3 the same cornual scarring was found. The left tube was otherwise normal. The right tube was also blocked at the fimbria. In the third successful case the block was limited to the cornua, as in Case 1.

In the other 2 cases with implantation into the uterus in which no pregnancy resulted, the cornua and the fimbriated ends of both tubes were involved, and according to the history the patients had had a much more severe post-partum infection. In the other 18 cases the fimbrial end of the tube was blocked by either gonorrheal infection or a pelvic peritonitis due to a ruptured appendix.

the original infection the tube is abnormal and pregnancy impossible or, if pregnancy occurs, ectopic pregnancy is common.

The findings on the 23 patients operated upon are given in Table 1. In the 3 successful cases that resulted in living infants cornual resection and tubal implantation were performed. These cases are briefly presented below.

TABLE 1. *Results of Operation in 23 Cases.*

CASE NO.	PATIENT	AGE	YEARS MARRIED	ETIOLOGY	PATHOLOGY	RESULT OF RUBIN TEST PREOPERATIVELY
		yr.				
1	V. K.	31	8	Sepsis after miscarriage	Bilateral cornual fibrosis	Tubes closed
2	R. U.	33	9	Salpingitis isthmica nodosa	Block at cornu, bilateral	Tubes closed
3	F. G.	30	2½	Peritonitis	Bilateral block at cornu; right fimbria closed.	Tubes closed
4	C. A.	33	5	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges and cornual block	—
5	R. M.	24	1	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
6	J. W.	31	1½	Gonococcal pelvic inflammatory disease	Left tubo-ovarian abscess; hydrosalpinx.	Tubes closed
7	P. G.	29	4	Gonococcal pelvic inflammatory disease	Adhesions; bilateral hydrosalpinges.	—
8	B. E.	25	½	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
9	V. K.	28	5	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	Tubes closed
10	P. N.	31	5	Gonococcal pelvic inflammatory disease	Right tube gone; left hydrosalpinx.	Tubes closed
11	M. L.	23	2	Gonococcal pelvic inflammatory disease	Left hydrosalpinx	—
12	L. S.	19	S	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
13	E. P.	22	1½	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges	—
14	E. M. O.	23	1	Gonococcal pelvic inflammatory disease	Bilateral hydrosalpinges; block at cornu.	Tubes closed
15	E. T.	35	12	Gonococcal pelvic inflammatory disease	Right tube and ovary gone; left hydrosalpinx; second operation — left tube closed.	Tubes closed
16	R. S.	19	— (single)	Gonococcal pelvic inflammatory disease	Right hydrosalpinx and cornual block; left hydrosalpinx.	—
17	M. D.	33	6	Post-partum infection	First operation, adhesions and bilateral hydrosalpinges; second operation, bilateral cornual block.	Tubes closed
18	F. K.	34	8	Pelvic inflammatory disease after miscarriage	Bilateral hydrosalpinges; 2.5 cm. from cornu on right.	—
19	A. L.	20	2	Post-partum pelvic inflammatory disease	Bilateral hydrosalpinges	—
20	L. T.	26	10	Pelvic inflammatory disease after miscarriage	Pregnancy in right tube; left hydrosalpinx.	—
21	J. C.	33	5	Post-partum pelvic inflammatory disease	Right hydrosalpinx; left tubo-ovarian abscess.	—
22	A. C.	34	13	Post-appendectomy peritonitis	Right tube and ovary previously removed; left hydrosalpinx.	Tube opened with air
23	A. T.	31	11	Post-appendectomy peritonitis	Right tubo-ovarian abscess; left hydrosalpinx.	Tubes closed

*Three years later a total hysterectomy and bilateral salpingectomy were performed.

These tubes were difficult to operate upon, and patency was obtained in only 6 of this group. Such a poor result is probably due to the fact that gonorrheal infection has been shown to travel across the endometrium and endosalpinx and then to invade the deeper layers. Microscopical examination of the acutely inflamed tube shows why the damage is so extensive and why even years after

CASE REPORTS

CASE 1. V. K., a 31-year-old woman who had been married 8 years, had 2 living children — aged 7 and 5. She had lost 2 children at the ages of 3 and 8 months, and had had a miscarriage at 3 months. Severe puerperal fever developed 2½ years before the studies began. The infection subsided after 2 months' hospitalization and 3 months' rest at home. Conception failed to occur thereafter.

Physical examination was negative except for a cervical laceration and a retroversion. Over an interval of months

three Rubin tests were done, and the tubes were found to be completely blocked. A uterosalpingogram showed the occlusion to be at the cornua. The husband had a normal physical examination and semen specimen. At operation the uterus was retrocessed, and there were numerous fibrous adhesions about both tubes. The tubes were patent and normal except for a fibrous, densely scarred portion at the junction of the tubes and the uterus. Resection of the cornua and implantation of the distal tube was done. A Rubin test 4 weeks postoperatively demonstrated the tubes to be wide open. The patient conceived 2 months postoperatively and has been delivered. This patient obviously had an excellent prognosis since the cause of the block was definitely known and both she and her husband had previously been very fertile.

Case 2. F. G., a 30-year-old woman who had been married 2½ years had had no pregnancies. She had had pelvic peritonitis before her marriage, and a uterosalpingogram showed blocked tubes prior to the studies under consideration. Physical examination was negative. The Rubin test failed to demonstrate patency. Repeat x-ray studies showed a normal uterine cavity, but no filling of the tubes. The husband had a normal semen specimen. At operation she had many adhesions, and there was obliteration of both tubes at the cornua. The right tube was closed at the fimbriated end. This was opened. The cornua were excised bilaterally, and the tubes implanted into the uterus. Four weeks postoperatively the Rubin test demonstrated patency. A repeat test was equivocal, and a uterosalpingogram was unsatisfactory. The patient adopted a baby 18 months after operation and 1 month later conceived. She was delivered 9 months later by cesarean section.

Table 1 (*Continued*).

Case No.	Result of Uterosalpingogram	Type of Operation	Result of Rubin Test Postoperatively	Postoperative X-Ray Study	Result of Operation
1	No oil left uterus	Implantation of both tubes	Tubes open	—	Pregnancy
2	Block at cornua	Implantation of both tubes	Tubes open	Right tube open; left closed.	Pregnancy 4 yr. later
3	Block at cornua	Implantation	Tubes open	Equivocal	Pregnancy
4	—	Implantation of right tube and salpingostomy; left salpingectomy.	—	—	—
5	—	Fish-mouth plastic	—	Right tube patent	—
6	Tubes closed	Fish-mouth plastic; salpingostomy.	Tubes closed	—	—
7	—	Bilateral salpingostomies	Tubes closed	Tubes closed	—
8	—	Bilateral salpingostomies	—	—	—
9	Bilateral hydrosalpinges	Bilateral salpingostomies	Tubes open	—	—
10	Left hydrosalpinx	Left salpingostomy	Tubes open	Tubes closed	—
11	Left hydrosalpinx	Right salpingectomy; left salpingostomy.	—	—	—
12	—	Bilateral salpingostomy	—	—	—
13	? patency; films misread.	Bilateral salpingostomies	—	—	—
14	Both tubes blocked at cornua	Bilateral salpingostomies	Tubes closed	Tubes closed	—
15	Left hydrosalpinx	Salpingostomy; myomectomy. Estes operation	Tubes closed —	— —	— —
16	—	Right salpingectomy; left salpingostomy.	Tubes closed	—	—
17	No filling of either tube	Lysis of adhesions and salpingostomy; bilateral tubouterine implantation.	Tubes closed	No filling of either tube	—
18	—	Bilateral salpingostomies; myomectomy.	Tubes closed	Left tube freely patent	—*
19	—	Left salpingectomy; right salpingostomy.	—	—	—
20	—	Right salpingectomy; left salpingostomy.	Tubes closed	—	—
21	—	Right salpingostomy; left salpingectomy.	—	—	—
22	Left hydrosalpinx	Salpingostomy	Tube open	—	—
23	Bilateral hydrosalpinx	Salpingostomy	Tubes open	—	—

Case 3. R. U., a 33-year-old woman, had been married 9 years, had had no pregnancies and had no history of pelvic inflammation. Her menstrual cycle was regular. Biopsy showed a secretory endometrium. Rubin tests failed to demonstrate tubal patency on repeated examinations. A uterosalpingogram showed both tubes blocked at the cornua by nodules suggestive of salpingitis isthmica nodosa. The husband had an excellent semen examination. At operation both tubes were blocked 1.9 cm. from the fundus. The obstructed tubes were resected into the endometrial cavity, and the remaining patent tubes sutured into the uterus.

A Rubin test postoperatively demonstrated patency, and the patient experienced shoulder pain. A uterosalpingogram showed the right tube open and the left tube blocked. Four years later she conceived and had a normal delivery.

Discussion

Before surgery is contemplated for treatment of tubal occlusion both husband and wife must be completely studied. The diagnosis of occlusion must be well established, preferably by both a Rubin test and a uterosalpingogram. There should be no history of tuberculosis, and the pelvic inflammatory disease, if present, should be in a chronic, quiescent stage, with no fever or leukocytosis. Observation over several months is indicated, during which conservative treatment is carried out. The woman should be otherwise in good health, with a negative physical examination. The husband must have been studied and must be fertile. After these studies operation for tubal occlusion can be recommended with full realization that success does not crown every effort. The gratitude of the patient who does become pregnant, however, affords impetus for further attempts.

264 Beacon Street

References

1. Rubin, I. C. Nonoperative determination of patency in fallopian tube in sterility. *J. A. M. A.* **74**:1017, 1920.
2. Solomons, B. Conservative therapy of pathological conditions of fallopian tube. *J. Obst. & Gynaec., Brit. Emp.* **43**:619-633, 1936.
3. *Idem.* Sterility, with special reference to surgical possibilities. *Surg., Gynec. & Obst.* **60**:352-362, 1936.
4. Bonney, V. Fruits of conservatism. *J. Obst. & Gynaec., Brit. Emp.* **44**:1-12, 1937.
5. Holden, F. C., and Sovak, F. W. Reconstruction of oviducts: improved technic with report of cases. *Am. J. Obst. & Gynec.* **24**:684-695, 1932.
6. Watkins, T. J. Discussion. Salpingostomy and pregnancy. *Am. J. Obst.* **64**:134, 1911.
7. Shaw, H. N. Pregnancy following implantation of outer end of only remaining fallopian tube into uterine cornu after resection of cornual pregnancy. *Bull. Johns Hopkins Hosp.* **32**:305, 1921.
8. Sovak, F. W. Tubal pregnancy in case of bilateral tubal implantation, with inspection of operative site after 3 years. *Am. J. Obst. & Gynec.* **32**:344-346, 1936.
9. *Die Krankheiten der Eileiter.* Edited by A. Martin. 427 pp. Leipzig: E. Besold, 1895.
10. Mackenrodt, A. Berichte aus Gynäkol. Gesellschaften. u. Krankheiten. *Zentralbl. f. Gynäk.* **18**:826, 1894.
11. Bland. Cited by Greenhill, J. O. Evaluation of salpingostomy and tubal implantation for treatment of sterility. *Am. J. Obst. & Gynec.* **33**:39-51, 1937.
12. Child, C. G. Sterility and conception. In *Gynecological and Obstetrical Monographs: A clinical presentation of pelvic pathology, by prominent American authorities.* 2877 pp. New York: D. Appleton-Century Co., 1922. P. 196.
13. Siegler, S. L. *Fertility in Women: Causes, diagnosis and treatment of impaired fertility.* 450 pp. Philadelphia: J. P. Lippincott Co., 1944.

Additional Reference

Isbruch, F. Die Möglichkeit der Beeinflussung geeigneter Fälle von primärer weiblicher Sterilität durch operative Massnahmen am Ovarium und am Tubenostinum. *Zentralbl. f. Gynäk.* **50**:1705-1720, 1926.

STREPTOMYCIN IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS*

Review of the Literature and Report of a Case Caused by Bacteroides

Robert Wallach, M.D.,† and Norman Pomerantz, M.D.‡

NEW YORK CITY

UP TO the present there have been scattered reports on the use of streptomycin in the treatment of subacute bacterial endocarditis. No individual series of cases has been large enough from which to draw conclusions. It is the purpose of this paper to present another unusual case of subacute bacterial endocarditis successfully treated with streptomycin, and to summarize the literature on the subject to May, 1949.

After several unencouraging reports, Loewe et al.,[1] 1944, showed that subacute bacterial endocarditis could be cured by penicillin given in sufficiently high doses for adequate lengths of time. Prior to this the prognosis in subacute bacterial endocarditis had been almost hopeless; subsequently the recovery rate has become approximately 80 per cent. In an effort to reduce further the 20 per cent failure rate other antibiotics have been sought for and tested. Since most of the failures are due to penicillin-resistant streptococci and to gram-negative bacilli, both of which are often sensitive to streptomycin, this agent, next to penicillin, has proved most useful in the treatment of the disease. The first reports of streptomycin-treated subacute bacterial endocarditis appeared in 1946. In the ensuing three years and up until May, 1949, 49 cases treated wholly or partly with streptomycin have been reported in the literature.

*From the Department of Medicine, New York Polyclinic Medical School and Hospital.

†Instructor, New York Polyclinic Medical School and Hospital.

‡Resident, New York Polyclinic Medical School and Hospital.

Review of the Literature

Of the 49 cases, 28 were treated successfully. In the great majority of cases both penicillin and streptomycin were used. It was often difficult to attribute the successful outcome to either of the drugs or to a combination of both. In some cases it was possible to say that streptomycin was the decisive factor because of the progressively downhill course that had preceded its use.

Seventeen different organisms were encountered. There were 33 gram-positive organisms, of which 18 responded to treatment, and 18 gram-negative organisms, of which 12 responded to treatment. (In 2 cases[2] there were mixed infections.) In vitro

sensitivity tests, although not completely dependable, can give a fair estimate of the prognosis but are not helpful in determining the dosage necessary for treatment. Thirty-eight organisms were tested for streptomycin sensitivity; 31 were found to be sensitive to 9 units or less per cubic centimeter, and of these, 21 were treated successfully. Seven were found to be sensitive to more than 9 units per cubic centimeter, and of these only 1 was treated successfully.

The range of streptomycin dosage varied widely. In some of the earlier cases small dosages for short periods were used because of the scarcity of the drug, and, remarkably enough, some of these patients recovered. In general the dosage used and the that followed an unfavorable response to large doses of penicillin.

Case Report

P. R., a 53-year-old waiter, was admitted to the New York Polyclinic Medical School and Hospital on December 2, 1947, because of increasing fatigue of 6 months' duration. Except for an occasional sore throat or pain in the knees he had been well until the previous July, when his remaining upper teeth had been extracted for replacement by a denture. Shortly after this he noticed increasing fatigue and weakness. Three weeks before admission he started to have fever, night sweats and chilly sensations; however, he continued to work. One week before admission he was forced to discontinue work because of weakness. He received seven daily injections of 300,000 units of penicillin in oil and wax without any appreciable effect on the fever, fatigue or night sweats.

Although he does not remember ever having had rheumatic fever, he knew that he had "murmurs of the heart" since childhood. He had had malaria at the age of 12, a tonsilectomy at 49 and a submucous resection at 51 years of age.

Physical examination disclosed a well developed, fairly well nourished man of asthenic habitus. He appeared acutely ill. Close scrutiny of the skin and mucous membranes revealed no petechiae. The eyes, ears, nose, mouth and throat were normal except for the presence of an upper denture. The lungs were clear. The heart was enlarged, and the rhythm regular, and presystolic and systolic murmurs were heard at the apex. The liver and spleen were not palpable. The extremities were normal.

Examination of the blood showed a red-cell count of 3,650,000, with a hemoglobin of 72 per cent, and a white-cell count of 8000, with 65 per cent neutrophils, 34 per cent lymphocytes and 1 per cent eosinophils. Urinalysis was normal except for a faint trace of albumin; the sediment contained no red blood cells. The sedimentation rate (Westergren method) was 30 mm. in 1 hour, and the icteric index was 10. Blood cultures taken on the 2nd, 3rd and 9th hospital days were negative. Urinalysis repeated on the 29th and 31st days demonstrated no red blood cells in the sediment. A roentgenogram of the chest showed emphysema of the lungs and a globular-shaped heart whose borders extended to the right and the left.

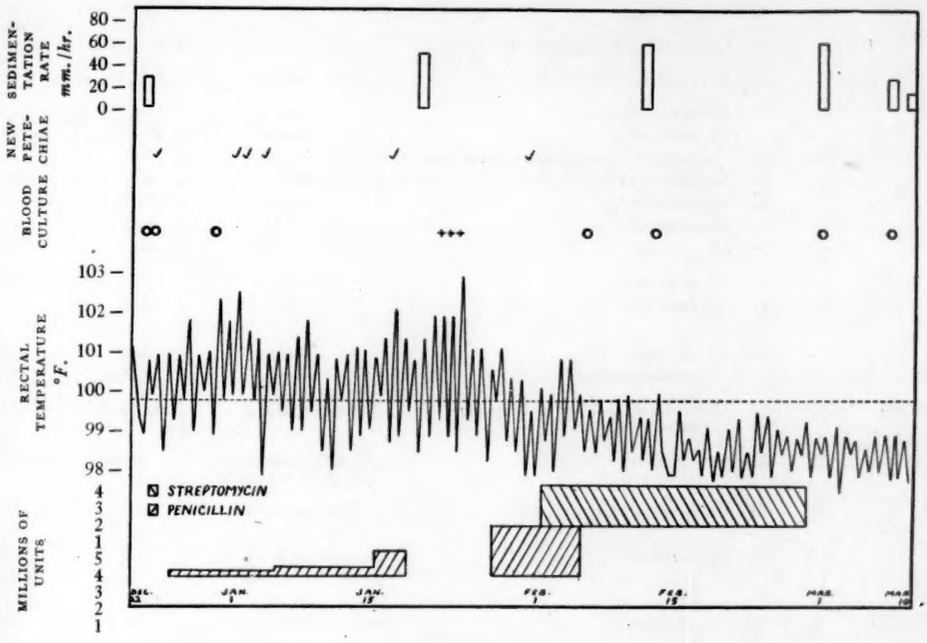

FIGURE 1. *Effect of Streptomycin Therapy in a Case of Subacute Bacterial Endocarditis.*

length of time treatment was continued were less than that advocated for penicillin. This is fortunate because of the uniformity of appearance of toxic symptoms. In all the cases in which this was alluded to it was noted that such symptoms did appear and were frequently permanent. The decision when to discontinue streptomycin in the face of a favorable response and the appearance of toxic symptoms remains a difficult one. This is even more so because bacterial sensitivity to streptomycin decreases rapidly, unlike that to penicillin.

The pertinent features of these cases are summarized in Table 1.

An unusual case of subacute bacterial endocarditis is presented below because the causative organism, a bacteroid, is rare in endocarditis, and because of the favorable response to streptomycin

TABLE 1. *Pertinent Features of Cases of Subacute Bacterial Endocarditis Reported in the Literature.*

CASE No.	AUTHOR	AGE	SEX	ORGANISM	PENICILLIN SENSITIVITY	STREPTOMYCIN SENSITIVITY	PENICILLIN THERAPY	
		yr.			units/cc.	units/cc.	units	days
1	Priest & McGee[3]	36	M	*Streptococcus viridans*	0.8	0.1	500,000	35
							1,000,000	42
							1,500,000	28
							2,000,000	—
2	Priest & McGee[3]	55	M	Nonhemolytic streptococcus	4.0	1.0	500,000	49
							2,000,000	42
3	Priest & McGee[3]	42	M	Nonhemolytic streptococcus	6.0	1.0	1,000,000	28
							2,000,000	9
4	Hunter & Duane[4]	40	M	Unidentified gram-negative bacillus	—	3.75	500,000	3
5	Cady et al.[5, 6]	78	M	*Streptococcus faecalis*	Over 1.0	—	240,000	10
6	Hunter[7]	57	M	*Pseudomonas aeruginosa* (*Bacillus pyocyaneus*)	—	15.0	—	—
7	Hunter[7]	51	M	Unidentified gram-negative bacillus	—	2.0	1.600,000	—
8	Hunter[7]	49	M	Hemolytic streptococcus	3.0	8.0	5,000,000	12
							10,000,000	14
							10,000,000	14
9	Hunter[7]	26	F	*Str. faecalis*	8.0	3.5	4,000,000	28
10	Hunter[7]	68	M	*Str. viridans*	1.0	20.0	5,600,000	21
							20,000,000	16
11	Hunter[7]	—	—	Unidentified gram-negative bacillus	—	1.0–16.0	—	—
12	Hunter[7]	—	—	*Haemophilus influenzae*	—	1.5–2.0	—	—
13	Hunter[7]	—		*Aerobacter aerogenes*	—	—	—	—
14	Hunter[7]	—		*Ps. aeruginosa*	—	40.0	—	—
15	Hunter[7]	—		Unidentified gram-negative bacillus	—	7.0	—	—
16	Hunter[7]	—	—	*Staphylococcus aureus*	10.0	0.4	—	—
17	Hunter[7]	—	—	*Str. viridans*	—	5.0	—	—
18	Hunter[7]	—	—	*Str. viridans*	—	5.0	—	—
19	Hunter[7]	—	—	*Str. viridans*	—	—	—	—
20	Hunter[7]	—	—	*Str. viridans*	—	—	—	—
21	Hunter[7]	—	—	*Str. faecalis*	—	4.0	—	—
22	Hunter[7]	—	—	*Str. faecalis*	—	—	—	—
23	Bland & Peterson[8]	32	F	*H. para-influenzae*	—	2.0	1,000,000	8
24	Appelbaum & Gelfand[9]	29	M	Gram-negative bacillus of genus Pasteurella	Over 20.0	Over 25.0	200,000	1
							800,000	4
							300,000	3
25	Doret & Saegesser[10]	26	M	*Str. viridans*	50 times less than standard organism	—	109,000,000*	240
26	Wise & Miller[11]	31	M	*Pasteurella tularensis*	—	—	800,000	12
27	Solari et al.[12]	—	—	—	—	—	—	—
28	Muller at al.[13]	25	F	*Str. viridans*	4.0	1.0	800,000	5
							1,600,000	4
							2,000,000	6
							1,600,000	6
29	McGarvey & Ernstene[14]	42	M	*Str. viridans*	0.03	—	300,000	21
							600,000	42
							600,000	25
30	McGarvey & Ernstene[14]	45	F	*Str. viridans*	0.25	—	600,000	5
							1,200,000	35
31	Olinger[8]	26	M	*Str. viridans*;	0.02		400,000	9
				diphtheroids.	0.1	0.6	800,000	33
32	Olinger[8]	39	F	*Str. viridans*;	0.2	8.0	2,400,000	56
				H. para-influenzae.	2.5	0.8		
33	Massell et al.[15]	9	F	Gram-negative coccobacillus (genus Hemophilus)	Over 10.0	4.0	—	—
34	Pearsall et al.[16]	31	F	*Str. faecalis*	Complete resistance	3.0	12,000,000*	15
35	Pearsall et al.[16]	41	F	*Str. viridans* (mitis strain)	Complete resistance	3.0	6,800,000*	17
36	Pearsall et al.[16]	19	F	*Str. viridans* (mitis strain)	Complete resistance	3.0	8,000,000	11
37	Guss[17]	50	F	*Str. faecalis*	Over 5.0	6.0	400,000	2
							800,000	2
							2,000,000	
38	Clark et al.[18]	43	M	Nonhemolyticus streptococcus	0.4	5.0	1,000,000	11
							2,400,000	17
							5,000,000	14
							5,000,000	8
							5,000,000	6
							8,000,000	52
39	Rachmilewitz & Fried[19]	18	M	*Str. viridans*	0.2	9.0	—	—
40	McCoy & Meyer[20]	—	—	*Neisseria subflava*	—	0.5	—	—
41	McCoy & Meyer[20]	—	—	*Escherichia coli*	—	1000.0	—	—
42	McCoy & Meyer[20]	—	—	*H. influenzae*	—	0.6	—	—
43	McCoy & Meyer[20]	—	—	*Corynebacterium*	1.0	5.0	—	—
44	Bell[21]	31	F	*Str. viridans*	—	—	0.8	—
45	DeMuth & Rawson[22]	40	M	*Ps. aeruginosa*	Over 10.0	500.0	0.8	15
46	Cressy et al.[23]	46	M	Bacteroides	—	—	1.1	13
							10.0	5
47	Cressy et al.[23]	75	M	*Str. viridans*	3.0	100.0	0.4	31
							1.2	12
48	Stuart-Harris et al.[24]	28	M	*Str. viridans*	0.03	0.25	210,000,000*	180
49	Stuart-Harris et al.[24]	34	F	*Str. viridans*	Over 4.0	1.5	300,000,000*	150
50	Leaman et al.[25]	25	F	*Str. faecalis*	1.25	—	1.0	11
							4.0	66

*Total.

TABLE 1 (*Continued*).

CASE No.	STREPTOMYCIN THERAPY		RESULT	REMARKS
	gm.	*days*		
1	0.5	5	Death	Culture of heart valves at autopsy sterile; streptomycin given just before death.
2	0.5	21	Cure	Blood cultures remained positive after treatment with streptomycin was stopped, but patient recovered and has been well for 9 mo.; cause of cure is questionable.
3	0.5 0.2 0.4	11 45 17	Cure	Blood cultures positive before streptomycin was started; cure can be attributed to streptomycin. Follow-up study for 6 mo.
4	3.0	10	Cure	Sulfadiazine also given; cure can be attributed to streptomycin. Follow-up study for 9 mo.; toxic febrile reaction to streptomycin.
5	3.2 2.0	3 6	Death	—
6	3.0 4.0 **6.0**	14 5 **7**	Death	—
7	3.0	21	Cure	Cure can be attributed to streptomycin; follow-up study for 2 mo. Toxic symptoms of dizziness and unsteady gait.
8	3.0	14	Death	—
9	4.0	28	Cure	Penicillin and streptomycin given concurrently; follow-up study for 10 mo. Toxic symptoms of dizziness and unsteady gait.
10	6.0	7	Death	Resistance of organism to penicillin and streptomycin increased greatly during therapy.
11	2.5	40	Death	Resistance of organism to streptomycin increased greatly during therapy; vestibular and auditory toxic symptoms.
12	2.0	10	Cure	Penicillin and sulfadiazine also given; cure can probably be attributed to combination of streptomycin and sulfadiazine.
13	**2.0**	**7**	Death	—
14	2.0–4.0	24	Death	—
15	2.6–3.2	20	Cure	Penicillin also given; it is not possible to say which drug effected cure.
16	1.5–3.0	28	Cure	Vestibular and auditory toxic symptoms
17	2.0	14	Death	—
18	3.0	34	Cure	Follow-up study for 3 mo.; vestibular toxic symptoms.
19	3.0 1.0	1 15	Cure	Follow-up study for 3 mo.
20	2.0	17	Death	—
21	4.0 1.0–8.0	5 28	Death	3-mo. remission between 2 courses of streptomycin; resistance of organism to streptomycin increased greatly during second course; toxic symptoms of fever and prostration.
22	3.0	32	Death	—
23	2.4 4.2	3 10	Cure	Cure can be attributed to streptomycin; toxic symptoms of vestibular and skin rash.
24	1.5 4.0	13 14	Cure	Sulfadiazine also used; follow-up study for 3½ mo.; cure can be attributed to streptomycin.
25	1.0 3.0 2.0	1 6 6	Cure	Cure can be attributed to streptomycin
26	0.8	8	Cure	Diagnosis based on tick bite and positive agglutination test (1:3200); blood cultures negative.
27	**—**	**—**	—	—
28	2.0	7	Death	Blood cultures positive before and negative after streptomycin was started; patient died of congestive heart failure.
29	4.0	5	Cure	Streptomycin given together with last course of penicillin; blood culture positive before last course; streptomycin decisive factor in this cure. Follow-up study for 14 mo.
30	4.0	7½	Cure	Streptomycin given together with last course of penicillin; blood culture positive before last course; streptomycin decisive factor in this cure.
31	2.0	6	Cure	Cultures negative and temperature normal when streptomycin was started; effect of streptomycin doubtful.
32	4.0	10	Cure	Penicillin and streptomycin given concurrently; effect of streptomycin questionable; follow-up study for 1 yr.
33	2.0	6½	Cure	Follow-up study for 1 yr.; toxic febrile reaction.
34	49.0*	23	Cure	Follow-up study for 1 yr.; cure attributed to streptomycin.
35	36.0*	17	Cure	Follow-up study for 11 mo.; cure attributed to streptomycin.
36	42.0*	19	Death	After streptomycin therapy was started patient improved and blood cultures became negative; she died of subarachnoid hemorrhage.
37	1.5 3.0	1 19	Cure	Follow-up study for 6 mo.; cure can be attributed to streptomycin; toxic symptoms of dizziness and unsteady gait.
38	4.0 4.0 4.0	20 8 3	Cure	Cure attributed to penicillin
39	5.5	7½	Cure	Follow-up study for 10 mo.; patient also received penicillin, but cure was attributed to streptomycin.
40	192.0*	52	Cure	Follow-up study for 3 mo.
41	22.0*	10	Death	—
42	48.0	24	Cure	Follow-up study for 10 mo.
43	117.0*	42	Cure	Toxic symptom of skin rash
44	2.0	10	Cure	Follow-up study for 18 mo.
45	1.5	7	Death	4 abdominal operations in 8 mo.; bacteremia followed the last one.
46	4.0	16	Cure	Follow-up study for 3 mo.; toxic febrile reaction; cure attributed to streptomycin.
47	4.0	14	Death	Resistance of organism increased greatly during treatment.
48	72.5*	23	Cure	Failure for streptomycin; cure attributed to penicillin and caronamide.
49	34.5*	—	Cure	Failure for streptomycin; cure attributed to penicillin and caronamide.
50	4.0	10	Cure	Cure attributed to penicillin and caronamide

*Total.

The effect of streptomycin therapy is shown in Figure 1. On the 3rd hospital day two petechiae were found on the left buccal mucous membrane. On the 5th day penicillin, 500,000 units daily in divided doses every 3 hours, was begun. During the next 11 days the swinging temperature, night sweats and fatigue remained unchanged. New petechiae were found on three occasions, whereas the older ones faded. All were on the buccal mucosa. On the 16th day penicillin was increased to 800,000 units daily. For a few days the patient felt better and his appetite improved, but then he lapsed back to his previous state. On the 25th day the penicillin was increased to 2,400,000 units daily. On the next day two new petechiae appeared in the right conjunctiva, and one on the lower lip. Because it was believed that he was not making any progress, penicillin was discontinued on the 28th day.

Blood cultures were taken on the 32nd, 33rd and 34th days. After all therapy had been stopped the daily temperature spikes reached higher levels, and his general condition seemed to deteriorate more rapidly. On the 37th day it was believed that further delay might cause irreparable damage, and penicillin therapy was resumed, massive doses (5,000,000 units daily) being used. Although the temperature fell somewhat he remained otherwise unchanged and on the 41st day new petechiae appeared in the left conjunctiva. On the 42nd day the blood culture taken on the 32nd day was reported positive for bacteroids. Streptomycin, 4 gm. daily in divided doses every 3 hours, was then started and continued for 28 days. Four days later, on the 46th day, the penicillin was discontinued. From the 45th day (3 days after the start of streptomycin therapy) clinical improvement was marked. His appetite improved, and he became more alert. From the 49th day the temperature remained below 100°F. No new petechiae appeared after streptomycin had been started. Two blood cultures taken after the beginning of streptomycin therapy (47th and 53rd days) and two after its termination (69th and 76th days) were negative. During the 3rd week of therapy symptoms of streptomycin toxicity appeared. The patient complained of dizziness, but his hearing remained unimpaired. The dizziness persisted for 6 months. When last seen in May, 1949, 14 months after discharge, he was in excellent health and working although he still had a slight gait disturbance.

Discussion

The genus Bacteroides[26] is made up of gram-negative, obligate anerobes, which are motile or nonmotile rods without endospores. They may or may not require enriched culture mediums. Until recently they comprised an amorphous unclassified group. They are normally inhabitants of the mucous membranes of the intestinal tract and may be found in the apical abscesses of teeth. They are rarely the cause of endocarditis. Four cases have appeared in the literature since 1945. Three [27] were treated with penicillin — 2 successfully. The fourth[28] was treated with penicillin and streptomycin successfully, and the result attributed to streptomycin.

The organism isolated in the case reported above was found on three successive daily cultures. It was a minute gram-negative bacillus, which grew slowly and poorly on Kracke's blood culture medium. It also grew on Brewer's thioglycollate medium. It did not grow on blood agar under ordinary conditions but did grow sparsely on blood agar under 10 per cent carbon dioxide. Unfortunately, the organism died off before further bacteriologic studies or sensitivity tests could be done.

This man's illness most likely started with the extraction of his teeth six months before his admission. Penicillin in the amounts used inhibited the organism (as evidenced by the persistently negative blood cultures during its administration) but could not effect a cure. After five days of penicillin in massive doses (5,000,000 units per day) the temperature receded somewhat, but new petechiae continued to appear and clinical improvement was not evident. It was not until seven days after streptomycin therapy that the temperature remained persistently below 100°F. by rectum and clinical improvement was noted. Symptoms of streptomycin toxicity (vertigo) appeared during the third week and were very annoying for six months. The decision to continue streptomycin after the appearance of toxic symptoms was made because it was thought that this drug offered the only chance for recovery and because of the known loss of sensitivity that ensues when sublethal doses of streptomycin are used. When seen for follow-up examination fourteen months after discharge the patient had completely recovered and was able to work although he still had a mild gait disturbance.

Summary

The literature relating to subacute bacterial endocarditis treated with streptomycin is reviewed.

A case of subacute bacterial endocarditis caused by Bacteroides and successfully treated with streptomycin is reported.

References

1. Loewe, L., Rosenblatt, P., Greene, H. J., and Russell, M. Combined penicillin and heparin therapy of subacute bacterial endocarditis: report of seven consecutive successfully treated patients. *J. A. M. A.* **124**:144-149, 1944.
2. Olinger, M. G. Mixed infection in subacute bacterial endocarditis. *Arch. Int. Med.* **81**:334-341, 1948.
3. Priest, W. S., and McGee, C. J. Streptomycin in treatment of subacute bacterial endocarditis: report of three cases. *J. A. M. A.* **132**:124-126, 1946.
4. Hunter, T. H., and Duane, R. B., Jr. Subacute bacterial endocarditis due to gram negative organisms. *J. A. M. A.* **132**:209-211, 1946.
5. Cady, J. B., and Allen, W. H. Case of Streptococcus fecalis septicemia treated unsuccessfully with streptomycin. *Guthrie Clin. Bull.* **16**: 31-33, 1946.
6. Cady, J. B., and Hunter, A. L., Jr. Streptococcus fecalis septicemia: concluding report of case. *Guthrie Clin. Bull.* **16**:90-93, 1947.
7. Hunter, T. H. Use of streptomycin in treatment of bacterial endocarditis. *Am. J. Med.* **2**:436-442, 1947.
8. Bland, E. F., and Peterson, E. W. Subacute bacterial endocarditis. *Am. Practitioner* **1**:498-504, 1947.
9. Appelbaum, E., and Gelfand, M. Case of bacteremia due to unidentified gram-negative pasteurella-like bacillus with recovery following streptomycin therapy. *Ann. Int. Med.* **26**:780-783, 1947.
10. Doret, J. P., and Saegesser, F. Stérilisation d'une endocardite lente par la streptomycine après échec de la pénicilline. *Rev. méd. de la Suisse Romande* **67**:443-447, 1947.
11. Wise, A. W., and Miller, W. A. Subacute bacterial endocarditis due to B. tularense, treated by streptomycin. *Illinois M. J.* **92**:182, 1947.
12. Solari, A. V., Polak, C., and Canepa, L. Endocarditis bacteriana subaguda; su tratamiento por acción combinada de penicilina, estreptomicina y penicilina. *Semana méd.* **54**:677-680, 1947.
13. Muller, B., Bayon, A., and Errard, L. Endocardite maligne lente à streptocoque viridans très résistant à la pénicilline. Négativation de l'hémoculture par l'emploi de la streptomycine. *Bull. et mém. Soc. méd. d. hôp. de Paris* **63**:883-886, 1947.
14. McGarvey, C. J., and Ernstene, A. C. Streptomycin for penicillin-resistant subacute bacterial endocarditis. *Cleveland Clin. Quart.* **15**:1-3, 1948.
15. Massell, B. F., Zeller, J. W., Dow, J. W., and Harting, D. Streptomycin treatment of bacterial endocarditis: report of case. *New Eng. J. Med.* **238**:464-466, 1948.
16. Pearsall, H. R., Pillow, R. P., and Wood, J. E., Jr. Observations on treatment of subacute bacterial endocarditis with penicillin and streptomycin. *Am. Practitioner* **2**:497-506, 1948.
17. Guss, J. H. Successful treatment of subacute bacterial endocarditis with streptomycin. *Am. Heart J.* **35**:662-664, 1948.

18. Clark, W. H., Bryner, S., and Rantz, L. A. Penicillin-resistant nonhemolytic streptococcal subacute bacterial endocarditis. *Am. J. Med.* **4**:671-689, 1948.

19. Rachmilewitz, M., and Fried, H. Streptomycin in treatment of subacute bacterial endocarditis. *Harefuah Tel Aviv* **34**:117-119, 1948.

20. McCoy, J. T., and Meyer, O. O. Treatment of subacute bacterial endocarditis with penicillin and with streptomycin. *Wisconsin M. J.* **47**:671-674, 1948.

21. Bell, J. N. Subacute bacterial endocarditis treated with streptomycin. *Illinois M. J.* **94**:119, 1948.

22. DeMuth, W. E., Jr., and Rawson, A. J. Pseudomonas septicemia and endocarditis: report of case. *Am. J. M. Sc.* **216**:195-202, 1948.

23. Cressy, N. L., Lahey, W. J., and Kunkel, P. Streptomycin in treatment of bacterial endocarditis: report of two cases. *New Eng. J. Med.* **239**:497-500, 1948.

24. Stuart-Harris, C. H., Colquhoun, J., and Brown, J. W. Penicillin and caronamide in resistant subacute bacterial endocarditis. *Lancet* **1**:99-101,1949.

25. Leaman, W. G., Wikingsson, M. B., Webster, M. B., and Shaw, C. C. Caronamide and penicillin subacute bacterial endocarditis due to Streptococcus faecalis. *Ann. Int. Med.* **30**:646-654, 1949.

26. Breed, R. S., Murray, E. G. D., and Hitchens, A. P. *Bergey's Manual of Determinative Bacteriology.* Sixth edition. 1529 pp. Baltimore: Williams & Wilkins Co., 1948. P. 564.

27. Tumulty, P. A., and Harvey, A. M. Experiences in management of subacute bacterial endocarditis treated with penicillin. *Am. J. Med.* **4**:37-54, 1948.

EVALUATION OF TOLSEROL IN THE TREATMENT OF CHILDREN WITH CEREBRAL PALSY*

ERIC DENHOFF, M.D.,† RAYMOND H. HOLDEN, M.A.,‡ AND CAROLL M. SILVER, M.D.§

PROVIDENCE, RHODE ISLAND

THE basic concept of the treatment of cerebral palsy is re-education in the form of physical and occupational therapy. This treatment might be enhanced if a drug were found that would favorably influence the disabilities peculiar to this syndrome. This drug should have a relaxing effect on spastic and athetoid states and should facilitate the correction of resulting deformities. Since such a therapeutic program cannot be successful without the co-operation of the patient, the drug would be even more valuable if it were to alter favorably the child's attitude and behavior.

Tolserol (3 o-toloxy 1,2-propanediol) has been reported to effect relaxation[1] and to act favorably upon behavior.[2] Although its action is more dramatic when the drug is administered intravenously, Berger and Schwartz[1] have reported a beneficial relaxant effect on muscle spasm, spasticity and rigidity and an ameliorating effect on tremor and involuntary movement of extrapyramidal origin when the drug is given in adequate oral dosage.[1] Since the drug is relatively nontoxic in this form and is palatable, it makes an attractive pharmacologic approach to the treatment of cerebral palsy in children.

Any new drug proposed as an adjunct to such treatment should be rigidly evaluated prior to its release for general use. Therefore, a study of young children with cerebral palsy was initiated in the hope that this drug might help improve their condition.¶

The purpose of this study is to evaluate the effect of tolserol on the child as a whole, as well as its specific action on the neuromuscular system. Inasmuch as many children with cerebral palsy frequently make slow but steady developmental progress in their early years, a legitimate criterion for benefit from the drug should be a more marked quantifiable improvement over a relatively short period.

MATERIALS AND METHODS

Subjects

Sixteen children with ages ranging from three to eight years who had been attending the Meeting Street School for Cerebral Palsy from four to ten months were selected for study. Fourteen cases were diagnosed as spastic, 1 as athetoid, and 1 as ataxic. In classification of neuromuscular dysfunction, 2 were considered severe, 11 moderate, and 3 mild.||

Experimental Procedure

All the children had been attending the school for at least three months before the beginning of the drug evaluation. In the period prior to the beginning of the study, all the subjects were given complete pediatric, neurologic, orthopedic and psychologic examinations, as well as personality ratings by experienced nursery-school teachers.

The subjects were divided into two groups. Those in Group I received the drug for three weeks, followed by a placebo mixture for another six weeks, and then the drug was readministered for another three-week period. In Group II, the procedure was reversed: a placebo mixture was given for the first three weeks, after which the drug was substituted for six weeks, and the placebo was given again for the last three weeks. This procedure provided both a three-week and a six-week period of evaluation, and was of great convenience in statistical evaluation.

*From the Meeting Street School for Cerebral Palsy.

†Medical director, Meeting Street School for Cerebral Palsy; director of Laboratory, Emma Pendleton Bradley Home, Riverside, Rhode Island.

‡Psychologist, Meeting Street School for Cerebral Palsy; junior psychologist, Emma Pendleton Bradley Home, Riverside, Rhode Island.

§Orthopedic consultant, Meeting Street School for Cerebral Palsy; junior assistant surgeon, Orthopedic Service, Rhode Island Hospital.

¶Tolserol was supplied through the courtesy of Dr. E. Sidney Newcomer, E. R. Squibb and Sons, New York City.

||A severe case was one in which the patient could not walk or utilize his hands with any degree of skill. A patient with a moderate case was one whose gait was decidedly deviant from normal and whose manual dexterity was impaired so that nursery-school tasks were performed with difficulty. A mild case was one in which gait and manual dexterity were functionally good, although lack of smoothness of movement was apparent.

Medication

Tolserol was prepared with aqueous propylene glycol and syrup of cherry* so that 30 cc. of the solution contained 1.0 gm. of the drug.[1] The dosage for each child was computed by Fried's rule based on a proportional amount according to body weight. The suggested adult dose was 1.0 gm. three to five times daily.[1] In this study the average dose was 33 mg. per pound of body weight per twenty-four hours. The tolserol mixture was administered to each child six times a day. The group that was serving as a control (that is, patients receiving the placebo) in each period was given a menstruum that was similar to the liquid tolserol in ingredients, color, taste and smell but did not contain the drug. The medications were coded so that none of the staff or the parents knew in which drug period each child was actually receiving myanesin. Since each child attended school only three days each week, the medication had to be administered mainly at home. The parents of each child recorded each dose in a notebook. Occasional lapses in dosage were due to illness.

Methods of Evaluation

Neurologic examination consisted of evaluation of cranial nerves (third, fourth, sixth, seventh and eleventh), reflexes and tests for co-ordination (Romberg, diadokokinesis, gait and movements). Reflexes were graded on a nine-point scale from +4 (markedly hyperactive) through 0 (normal) to —4 (absent).

Orthopedic examination consisted of evaluation of the following points: ability to stand or walk, or both, deformities of gait, grasping functions of upper extremities and absence or presence (and degree) of spasticity and contractures of extremities and trunk. A physical therapist and an occupational therapist supplemented the orthopedic examination by weekly progress reports.

Psychomotor tests evaluated performance in fine manipulation and gross movement. Wallin peg-boards A and B and the speed of placing ten marbles in a cup measured fine manipulation, whereas walking a measured distance (2½ yards) and up and down a flight of five stairs represented measures of gross bodily movement.

Personal-social rating scales were utilized to obtain objective measures of any behavioral changes. The records were completed by nursery-school teachers twice during each testing period. The nine items used rated sociability, activity control, noise-disturbance control, self-entertainment, co-operation in routine, work capacity, willingness to follow directions and mood swings. A similar rating scale was distributed to parents so that quantifiable data could be obtained of changes observed in the home surroundings. In addition, a daily behavior chart was maintained by the nursery-school teachers to record any outstanding behavior not included in the rating scales.

Laboratory studies were performed to determine possible toxic effects on the hematopoietic and genitourinary systems, before and after each drug period. These tests consisted of blood counts and urine examinations.

Criteria of Improvement

The criteria of improvement due to drug action were considered to be a primary relaxing effect as shown by improvement in neuromuscular status and greater ease in motor performance; and a secondary effect on behavior because of neuromuscular relaxation, which might well be shown by lessened hyperactivity, greater concentration and more facile social relationships — characteristics that children with cerebral palsy frequently lack. Ratings of "improved" were judged as follows: neurologic — improved co-ordination, less hyperactive reflexes and improved function of areas innervated by the third, fourth, sixth, seventh and eleventh cranial nerves; orthopedic — decrease in deformity or improved function, or both; psychomotor — improved performance on five tests; and behavior — decreased irritability and hyperactivity, or increased sociability, or both. Ratings of "worse" were judged as follows: neurologic — poorer co-ordination, more hyperactive reflexes and greater cranial-nerve impairment; orthopedic — increased degree of deformity or increased impairment of function, or both; psychomotor — less accurate test performance, and behavior — increased irritability and hyperactivity or decreased sociability, or both.

Results

There was no consistent outstanding, observable, over-all improvement in the children studied. One child improved in three of the methods of evaluation used, 7 improved in two, and 5 improved in one. On the other hand, 3 children showed no improvement or got worse in at least one category (Table 1).

Neurologic

Nine children (56.25 per cent) showed improvement. At the completion of the study, superficial and deep tendon reflexes were nearer normal, the Babinski reflex was lessened, and there was improvement in the Romberg sign and tests of co-ordination. Cranial-nerve action did not seem to be affected. Six children (37.5 per cent) became worse, and 1 (6.25 per cent) showed no change.

Orthopedic

Five children (31.25 per cent) showed slight improvement. In no case was a striking improvement

*Tolserol, 8.0, propylene glycol, 48.0, camphor water, 72.0, distilled water, 72.0, and syrup of cherry, as needed, 240.0.

noted. Two patients (12.5 per cent) became worse, and in 9 (56.25 per cent) there was no change.

Psychomotor

Five children (31.25 per cent) improved, 2 (12.5 per cent) became worse, and 9 (56.25 per cent) showed no change. Statistical analysis of group results demonstrated no significant difference between the group while the drug was being given and the group while the placebo was being given. All tests for fine motor co-ordination showed a slightly longer mean performance time, whereas tests for gross bodily movement showed a slightly faster mean performance time — neither significantly so, however.

Behavior

Three children (18.75 per cent) improved, 3 (18.75 per cent) became worse, and the remainder showed no changes in over-all behavior. More specifically, 7 children showed improvement in one but not more than two of the personal-social behavior items, whereas 6 were reported as worse in one or two items, and 3 showed no change. The behavior items affected were usually sociability, self-entertainment, elation and depression.

Laboratory Studies

There were no significant deviations from the normal in urine or blood counts either during administration of the drug or after the cessation of tolserol therapy.

Discussion

The results of this study proved interesting in several respects. Although there were no outstanding general improvements, there was evidence that the drug caused a diminution of exaggerated reflexes and some improvement in co-ordination. These results are in accord with those reported by Berger and Schwartz[1] and Gammon and Churchill.[2] However, this change in neurologic status did not seem to be reflected in improved over-all performance or in improved relaxation either immediately or later. Whether this was because insufficient dosage of the drug was given or because the clinical methods of testing behavior were not sufficiently sensitive to reflect minimal degree of improvement is difficult to state.

It has been the experience with curare, which has also been used to facilitate relaxation in cerebral palsy, that the degree of orthopedic improvement, when it occurs, is measurable, even though the effect may be transient.[3] With tolserol, this grossly relaxant effect was observed neither by the orthopedic surgeon in his examinations nor by the physical therapist in her tri-weekly therapeutic periods. Thus, although in 5 cases there was improvement from the orthopedic standpoint, the improvement was invariably slight and not of appreciable degree in any case. It is also of note that in 2 cases (12.5 per cent) the patients became definitely worse orthopedically while on tolserol therapy.

Performance time on tests of fine manipulation tended to be slightly slower on the drug, whereas in tests for gross bodily movement the time was somewhat faster. However, in neither case were the results statistically different from those of the control group.

Since it is recognized that parents and workers tend to be overly enthusiastic when they know a new drug is being administered, this study was designed to evaluate behavioral results of tolserol as objectively as possible and to minimize unwarranted conclusions based on subjective opinion alone. Nevertheless, great leeway was given both parents and nursery-school observers to report noticeable behavior changes in any way, and at the same time reports on objective behavior scales were required. In spite of the natural inclination for enthusiasm, in only 3 children could improved behavior be noted in the drug periods. Favorable behavioral changes might be expected, since one might assume that when a spastic child is relaxed he would feel happier or "lighter," a result obtained with a comparable group studied with curare.[4]

Table 1. *Pertinent Data and Summary of Results in 16 Children Who Received Tolserol.*

Case No.	Age		Diagnosis	Degree	Dose	Results			
						Neurologic	Orthopedic	Psychologic	Behavior
	yr.	mo.			gm./24 hr.				
1	3	3	Spastic diplegia	Moderate	1.3	Improvement	No change	No change	No change
2	2	8	Spastic diplegia	Moderate	0.96	Patient worse	Slight improvement	Slight improvement	No change
3	3	5	Spastic diplegia	Mild	0.96	Improvement	Slight improvement	Slight improvement	No change
4	3	7	Spastic monoplegia	Moderate	1.0	Improvement	No change	No change	Improvement
5	3	8	Spastic hemiplegia	Moderate	1.2	Patient worse	No change	No change	No change
6	4	8	Spastic hemiplegia	Moderate	1.4	No change	No change	Slight improvement	Improvement
7	4	6	Spastic hemiplegia	Moderate	1.3	Improvement	Patient worse	Patient worse	No change
8	5	3	Spastic hemiplegia	Moderate	1.2	Improvement	No change	No change	Improvement
9	4	1	Spastic hemiplegia	Mild	1.0	Improvement	Slight improvement	No change	No change
10	6	1	Spastic hemiplegia	Mild	1.9	Patient worse	No change	No change	Patient worse
11	3	2	Spastic quadriplegia	Moderate	1.1	Improvement	No change	No change	No change
12	3	7	Spastic quadriplegia	Moderate	1.2	Improvement	No change	Improvement	No change
13	8	6	Spastic quadriplegia	Severe	1.6	Patient worse	Patient worse	Patient worse	No change
14	6	6	Spastic quadriplegia	Severe	1.1	Patient worse	Slight improvement	No change	Patient worse
15	6	6	Athetosis	Moderate	1.4	Patient worse	No change	No change	No change
16	5	9	Ataxia	Moderate	1.3	Improvement	Slight improvement	Slight improvement	Patient worse

Three children who had been reluctant to participate in group activities for several months prior to administration did seem happier during the drug administration. On the other hand, a similar number of children became gloomy or withdrawn when they received the drug.

A liquid vehicle for administration is preferred since it has been shown experimentally that a higher drug concentration is obtained by this method and that absorption is much more uniform than by tablets.[5] The drug was given six times a day at two-hour intervals to ensure maximum concentration in the blood for at least twelve hours a day during each entire three-week period of administration. There were no observable toxic effects, although for the first few days a few children complained of nausea and abdominal pain. This effect was transient.

It is believed that the drug did not have a primary or secondary relaxing effect. It did have a specific beneficial relaxant effect on some children as shown by improved reflexes only, but improved behavior and performance were negligible. The methods utilized in this study were considered sufficiently sensitive to demonstrate any improvements had they been present. It is possible that the dosage was not sufficient to achieve adequate relaxation although the dosages employed were of the same relative magnitude as those recommended in the literature.[1] If this is so, further study should be initiated to ascertain the maximum dosage that can be tolerated in children of this age.

Summary

Sixteen children with cerebral palsy received tolserol in two three-week periods. No definite over-all improvement was noted.

Improvement was primarily in the neurologic category: 56.25 per cent of the children showed diminution of exaggerated reflexes, and 12.5 per cent became worse.

Orthopedic improvements were slight. Five patients (31.25 per cent) showed improvement, not marked, and 2 (12.5 per cent) became worse, 9 (56.25 per cent) showing no change.

Locomotion was improved somewhat in 6 cases (37.5 per cent).

Behavior changes were not appreciable.

The drug did not produce any noticeable toxic effects.

We are indebted to the staff and consultants of the Meeting Street School for their invaluable assistance in this research.

References

1. Berger, F. M., and Schwartz, R. P. Oral myanesin in treatment of spastic and hyperkinetic disorders. *J. A. M. A.* **137**:772-774, 1948.
2. Gammon, G. D., and Churchill, J. A. Effects of myanesin upon central nervous system. *Am. J. M. Sc.* **217**:143-148, 1949.
3. Schlesinger, E. B. Curare: review of its therapeutic effects and their physiological basis. *Am. J. Med.* **1**:518-530, 1946.
4. Denhoff, E., and Bradley, C. Curare treatment of spastic children: preliminary report. *New Eng. J. Med.* **226**:411-416, 1942.
5. Newcomer, E. S. Personal communication.

ORAL ADMINISTRATION OF AUREOMYCIN IN THE TREATMENT OF URINARY INFECTIONS*

Alexander M. Rutenburg, M.D.,† and Fritz B. Schweinburg, M.D.‡

BOSTON

In a previous communication[1] intramuscular injection of aureomycin hydrochloride was reported to be not only a highly effective antibiotic in a variety of urinary infections but also, in many cases, curative after other antibiotics had failed. Owing to the pain caused by the intramuscular injections, even when the drug is given in a 1 or 2 per cent procaine solution, a subsequent series of 26 patients were treated by aureomycin given orally.

Observations

These cases comprised an unselected group of 26 acute and chronic urinary infections and included 5 with chronic renal insufficiency. Seventeen patients had had prior treatment with other antibiotics without clinical or bacteriologic improvement. Twenty had one or more of the following complications: hydronephrosis, calculi, ureteral stricture and prostatic obstruction. Obstructive disease, if present, was treated during aureomycin therapy.

Twenty-one of the infections were due to a single organism, and 5 to more than one. The organisms involved were *Escherichia coli* (8 cases), *Aerobacter aerogenes* (12 cases), *Pseudomonas aeruginosa* (11 cases), *Proteus vulgaris* (1 case), hemolytic *Staphylococcus aureus* (1 case) and *Streptococcus faecalis* (1 case).

Two grams of aureomycin was given daily in divided doses for four to six days, or longer, so long as bacteria were present. If cure did not result in two weeks, the drug was discontinued.

Oral administration of aureomycin was generally well tolerated. In 3 patients with nausea and another with diarrhea, the reactions were mild, and the therapy was not interrupted. In 2 other patients

*From the Kirstein Laboratory for Surgical Research, Beth Israel Hospital, and the Department of Surgery, Harvard Medical School.
Aided by a grant from Lederle Laboratories Division of American Cyanamid Company, New York City.

†Kirstein Fellow in Surgery, Beth Israel Hospital; assistant resident in surgery, Beth Israel Hospital.

‡Research associate, Harvard Medical School; research bacteriologist, Beth Israel Hospital.

vomiting prevented oral therapy, and the drug was given parenterally. The reactions varied with different lots of the drug. With the more recent lots, no gastrointestinal symptoms occurred. Renal injury was not observed during treatment. The nonprotein nitrogen was not increased in patients with renal insufficiency. Shortly after the drug had been started the urinary pH dropped to 4.5 to 6.0 and remained within this range as long as the drug was administered. Catheter specimens were cultured every second day, and treatment was continued for two or three days after the first sterile specimen. The patients were followed for ten to thirty days and were considered cured only when two to five specimens of urine were found to be sterile after cessation of treatment. Anemia, leukopenia or thrombopenia did not develop. The white-cell counts, which had been elevated before treatment, dropped to normal values within one or two days when treatment was successful.

Results

The clinical symptoms disappeared in all patients in a surprisingly short period—usually within twenty-four to forty-eight hours. It is noteworthy that the clinical improvement occurred whether the urine had or had not become sterile. In cases in which bacteria persisted, the clinical symptoms usually recurred when the drug was discontinued. The urine became sterile in 16 cases and remained so after the drug was discontinued.

A close correlation was observed between the clinical result and the in vitro sensitivity of the organism to aureomycin. Thus, a rapid cure of the infection was obtained in every case in which the strain was sensitive, whereas partial or total therapeutic failure resulted when the strain was resistant.

The sensitivity of bacteria to a given antibiotic varies considerably, not only from species to species but also from strain to strain within a species. One hundred and thirty strains of various species, including many of those encountered in the present group of cases, were tested for sensitivity in vitro to aureomycin by the serial tube-dilution method.[1] This method tests the response of a twenty-four-hour broth culture inoculated with some 20,000 organisms of a particular strain to graded dilutions of the antibiotic. The lowest concentration of an antibiotic, in microgm. per cubic centimeter, that produces no macroscopically visible growth after incubation for twenty-four hours at 37°C. is considered the bactericidal titer. This titer for aureomycin was found to be as follows: the titer for thirty-five strains of *Ps. aeruginosa* varied from more than 200 to 0.0125 microgm. per cubic centimeter, over half the strains requiring more than 50 microgm. per cubic centimeter. The titer for thirty strains of *P. vulgaris* ranged from over 200 to 0.0125, a third of the strains requiring more than 50 microgm. per cubic centimeter. The titer of twenty-five strains of *Esch. coli* and of twenty strains of *A. aerogenes* ranged from 6.25 to 0.0125 microgm. per cubic centimeter, but with an occasional strain requiring more than 200. The titer of ten strains of hemolytic *Staph. aureus* and of ten strains of beta-hemolytic streptococcus were inhibited by 0.4 to 0.0125 microgm. per cubic centimeter. If the growth of a strain was completely inhibited by a concentration of less than 50 microgm. of aureomycin per cubic centimeter of culture, the strain was considered sensitive. If the growth was completely inhibited by a concentration of 50 microgm. or higher per cubic centimeter of culture, the strain was considered resistant.

There was recurrence of infection in 2 patients. The first had chronic urinary retention and acute pyelonephritis due to *A. aerogenes* that was very sensitive to aureomycin in vitro. He responded rapidly to aureomycin therapy, but twice at intervals of three weeks the infection recurred. Both relapses yielded promptly to the drug.

The second patient, with severe cardiovascular disease, renal tumor and a hypertrophied obstructing prostate, had an infection due to *Ps. aeruginosa* that was very sensitive to aureomycin in vitro. Twenty days after the drug had been discontinued the infection recurred and again responded rapidly to the drug.

In a third patient with chronic cystitis and pyelonephritis due to *Esch. coli*, as well as renal insufficiency and a blood nonprotein nitrogen varying from 80 to 120 mg. per 100 cc., the infection was cured within forty-eight hours. The urine remained sterile for twenty-eight days. Reinfection occurred with *A. aerogenes*. A second course of therapy promptly sterilized the urine, which remained sterile for the next fourteen weeks, when observation was discontinued.

In these 3 patients, bacterial resistance to aureomycin did not develop.

A fourth patient, with a vesicovaginal fistula and a mixed urinary infection due to *A. aerogenes*, *Str. faecalis* and *Ps. aeruginosa*, improved clinically, but only the first two of these organisms were cleared from the urine. *Ps. aeruginosa* remained. In a fifth patient with mixed infection, one organism (*A. aerogenes*) was cleared, but the other (*Ps. aeruginosa*) was not. This patient also showed clinical improvement.

There were 5 bacteriologic failures in monovalent infections, 1 due to *Esch. coli* and 4 to *Ps. aeruginosa*. In these cases the bacteria were resistant to aureomycin in vitro.

Of 34 strains of bacteria found in the urines of the 26 patients, all 12 strains of *A. aerogenes*, 7 or 8 strains of *Esch. coli* and 1 strain each of *P. vulgaris*, hemolytic *Staph. aureus* and *Str. faecalis*, were eliminated from the urine. Of 11 strains of *Ps. aeruginosa*, 5 that were sensitive to the drug

in vitro were eliminated, whereas 6 that were resistant in vitro were not.

Discussion

Sixteen of 26 patients were promptly cured by a single course of oral administration of aureomycin. Several courses were required in the 3 patients who had recurrence of infection. In these and in the patient with a vesicovaginal fistula, the underlying disease had not been dealt with successfully. Clinical improvement resulted in all the patients in this series, even in the 7 cases of failure to eradicate the bacteria (1 of *Esch. coli* and 6 of *Ps. aeruginosa*). There was exact correlation between bacterial sensitivity in vitro and the immediate bacteriologic response, regardless of whether the complicating disease was dealt with successfully. In the latter cases recurrences or reinfections were to be expected, and in fact occurred. Such patients cannot be permanently cured by any antibiotic. These results in *Ps. aeruginosa* infections are better than those reported by others.[2, 3] In 2 cases the strains that were resistant to aureomycin yielded to subsequent treatment with sulfamethazine[4] to which they were very sensitive in vitro. We have observed no case in which bacterial resistance to the drug developed during treatment.

Summary

In 26 patients with a variety of urinary infections due chiefly to gram-negative bacilli, aureomycin was as effective by oral as by intramuscular administration. Clinical improvement occurred in all cases. Bacteriologically, 19 patients, of whom 12 had failed to respond to other antibiotics and 13 had complicating disease in the urinary tract, were cured, 16 by a single course and 3 by repeated courses of therapy. *Pseudomonas aeruginosa* was the least susceptible of the bacteria encountered. Bacterial resistance did not develop.

We are indebted to Miss Annette Freedman for technical assistance.

References

1. Rutenburg, A. M., and Schweinburg, F. B. Aureomycin in urinary infections due to gram-negative organisms. *Proc. Soc. Exper. Biol. & Med.* **70**:464-466, 1949.
2. Finland, M., Collins, H. S., and Paine, T. F., Jr. Aureomycin, new antibiotic: results of laboratory studies and of clinical use in 100 cases of bacterial infections. *J. A. M. A.* **138**:946-949, 1948.
3. Long, P. H., Schoenbach, E. B., Bliss, E. A., Bryer, M. S., and Chandler, C. A. Experimental and clinical use of polymyxin, chloromycetin, and aureomycin. *California Med.* **20**:157-166, 1949.
4. Rutenburg, A. M., and Schweinburg, F. B. Sulfamethazine in treatment of urinary infections due to gram negative bacilli. *Surgery* **26**:215-222, 1949.

MEDICAL PROGRESS

HEMORRHAGIC DISEASES*

Walter B. Frommeyer, M.D.,† and Robert D. Epstein, M.D.‡

BIRMINGHAM, ALABAMA, AND YONKERS, NEW YORK

THE subject of hemorrhagic disease is considered under the general headings of problem in diagnosis, hypotheses concerning hemostasis in normal subjects, diagnostic procedures, history, physical examination, basic examination of blood, urine and stool, measurement of capillary fragility, bleeding time, platelet count, clot retraction, measurement of coagulation and clotting times of venous blood, clotting time of recalcified plasma, screening tests for abnormal coagulation, determination of prothrombin activity, prothrombin consumption and determination of fibrinolysis.

Problem in Diagnosis

The physician is called upon to diagnose and treat patients with signs and symptoms of an increased tendency to bleed. The manifestations of hemorrhagic diathesis are extremely variable, since abnormal bleeding may be evidenced as purpura in the skin, subcutaneous hemorrhage, bleeding from any mucous surface or hemorrhage into any structure or organ of the body.

Since the prognosis and treatment for the patient with hemorrhagic diathesis vary widely, it is essential to establish, as well as possible, the diagnosis or mechanism for the bleeding. This is done by at least two approaches. In the first place the patient is studied, a series of basic and screening examinations being used, in an attempt to establish a diagnosis of the primary illness, which may or may not be that of a primary hemorrhagic disease. Secondly, a series of special examinations of a biologic nature are made to evaluate qualitatively and quantitatively abnormalities of the *vascular defense* of the body and of the process of clot formation.

With these data, the underlying disease and the mechanism causing hemorrhage can be defined

*Adapted from *A Syllabus of Laboratory Examinations for Clinical Diagnosis* (in press) by permission of the Harvard University Press.

From the Thorndike Memorial Laboratory and the Second and Fourth Medical Services (Harvard), Boston City Hospital, and the Department of Medicine, Harvard Medical School.

†Instructor in medicine, Medical College of Alabama, University of Alabama.

‡Assistant in medicine, University Hospital, New York University—Bellevue Medical Center; clinical assistant physician, St. Joseph's Hospital, Yonkers, New York.

in part in such conditions as hereditary hemorrhagic telangiectasia, scurvy and hemophilia, conditions associated with extreme thrombocytopenia, hypoprothrombinemia and fibrinogenopenia and conditions associated with circulating anticoagulants and other abnormalities (Table 1).* In other cases, it is possible to indicate the abnormal mechanism responsible for bleeding, such as thrombocytopenia, even though the biologic effect of the abnormality may not be completely understood and the cause of thrombocytopenia may not be evident. Certain aspects of these tests are arbitrary, nonspecific, crude, poorly defined and limited in significance by a lack of understanding of some features of their mechanism. Also, there may be a lack of true correlation of certain results obtained in vitro with the symptoms and signs observed in vivo. For example, there may be thrombocytopenia with or without hemorrhagic diathesis; in hemophilia, bleeding may continue in a serious degree when the clotting time, as measured in glass tubes, has returned toward normal.

Hypotheses Concerning Hemostasis in Normal Subjects

Hemostasis is a term that by definition means halting the escape of blood. Hemostasis probably results from a combined effect of extravascular factors, such as location of the vessel and tone of the surrounding tissue; vascular factors, such as size and structure of the vessels as well as vascular tone; and factors of clot formation, such as the number of platelets and the amounts and state of the constituents of the blood required for proper blood coagulation. A defect in any one of these three factors may result in an alteration of hemostasis. In hemorrhagic diathesis, consideration is too often limited to the coagulation of blood itself. All three of the factors listed above must be considered and critically scrutinized when bleeding is not halted spontaneously. The critical reports of Quick,[1] Macfarlane,[2] Tocantins,[3] Zucker[4] and Zucker[5] contain detailed discussions of the experimental evidence and the hypotheses concerning hemostasis in the normal person and the alterations observed in disease. The theory of blood coagulation is discussed below.

In the normal subject, hemostasis following injury occurs spontaneously, presumably because of the following series of mechanisms, which are here outlined in an oversimplified manner. More detail is given in the sections describing special tests.

Extravascular Factors

When bleeding occurs from a vessel, such as a capillary, the hydrostatic pressure within the vessel falls and that in the surrounding tissue rises as a result of the outflow of blood from the ruptured vessel. The increase in tissue pressure in combination with normal tissue tone tends to reduce the flow of blood through, as well as from, the ruptured vessel.

Vascular Factors

After vascular rupture vasoconstriction and retraction of the vessel promptly occur. Vasoconstriction lasts for a few minutes or a longer period, tending thereby to occlude the lumen of the vessel. Retraction also tends to occlude the lumen by mechanically blocking the opening of the vessel by means of the surrounding tissue.

Factors of Clot Formation

Concomitantly with rupture of a vessel, blood escapes into the surrounding tissue and may be mixed with tissue factors that enhance clot formation. In the lumen of a ruptured vessel itself, platelets agglutinate and adhere to the area of broken intima. Fibrin is deposited about the platelets that disintegrate. This apparently enhances the formation of a clot, with subsequent retraction, so as to form a plug in the lumen of the vessel. If the clot formation is secure, hemostasis continues after the vessel is no longer constricted. The clot will then be organized or resolved with recanalization of the vessel.

Diagnostic Procedures for the Study of Patients with Hemorrhagic Diseases

It is recommended that the physician study a patient with hemorrhagic disease by means of a systematic approach from the basic and screening examinations to the more specialized tests, certain of which are discussed below in detail.

Basic and Screening Examinations

These include history, physical examination, basic examination of the blood (determination of hemoglobin or hematocrit, white-cell count and differential count, estimation of the number of platelets from the stained smear and serologic test for syphilis), basic examination of the urine and basic examination of the stool. From the initial study of the patient, a presumptive diagnosis can be made in certain cases of a disease complicated by hemorrhagic manifestations or of a primary hemorrhagic disease. The vascular defense and the process of clot formation are usually studied to aid further in diagnosis.

Special Tests Related to Vascular Defense and Clot Formation

Vascular defense and clot formation are determined by the following procedures: measurement of capillary fragility, bleeding time, platelet count, clot retraction, coagulation time, clotting time of recalcified plasma, screening tests for abnormal

*Deficiency of calcium of sufficient degree to interfere with the clotting mechanism is not compatible with life. Accordingly, hypocalcemia is not observed clinically as a cause of hemorrhagic disease.

TABLE 1. *Classification of Hemorrhagic Diseases, with Comments on Mechanism and Certain Laboratory Tests.*

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PROTHROMBIN CONCENTRATION	PROTHROMBIN CONSUMPTION
Hemorrhagic diseases associated with apparent abnormalities of *vascular bed* but with normal platelets and essentially normal blood coagulation:								
Hereditary hemorrhagic telangiectasia (Rendu, Osler, Weber disease) Localized areas of exposed, thin-walled capillaries	Non-sex-linked hereditary disease exhibiting telangiectatic lesions consisting of thin-walled, dilated capillaries that are exposed and may bleed from slight trauma. Some capillaries show wall consisting of endothelium only, with complete loss of supporting elastic tissue. Others reveal complete vascular wall with dilatation and exposure as only abnormalities. There are usually no symptoms in childhood; symptoms occur with increasing age in adults. Lesions may be located on skin or mucous membrane or in viscera. Patients may have no hemorrhage. Intermittent hemorrhage may occur externally or internally. There is no specific treatment.	Normal	Normal	Normal	Normal	Normal	Normal	Normal
"Thrombasthenia"; hereditary hemorrhagic diathesis; pseudohemophilia (von Willebrand and Glanzman).	Mechanism of bleeding is unknown but may be related to abnormal function of platelets or vascular malfunction such as poor vascular constriction following injury. Disorder may be familial and transmitted to either sex. There occurs persistent bleeding following minor trauma, bleeding gums, ecchymoses, melena, hematuria, epistaxis and, in females, menorrhagia and metrorrhagia. Hemarthroses have been reported but are rare. It is not known whether these cases represent disease entity or several diseases. There is no known treatment.	Markedly prolonged lor norma	Prolonged in some cases	May be reduced	Normal	Increased capillary fragility in about 50% of cases	Normal	No studies reported
Scurvy (decreased intercellular collagen substance)	Hemorrhage appears to result from lack of intercellular collagen substance due to *prolonged* deficiency in ascorbic acid and may be associated with purpura that is perifollicular or there may be large ecchymoses.	Normal	Normal	Normal	Normal	Marked increase in capillary fragility, but test returns to normal promptly after administration of vitamin C	Norma	Normal
Senile purpura; lack of supporting structures.	Rupture of capillaries presumably results owing to loss of elasticity and atrophy of supporting tissues. In senility it is not uncommon for purpura and hematomas to develop especially in dependent parts of body, with or without trauma.	May be slightly prolonged	Normal	Normal	Normal	Capillary fragility may be slightly increased	Normal	Normal
Sepsis (increased capillary fragility of toxic origin)	Although mechanism is unknown, it is thought that purpura results from defect in capillary wall, probably on toxic basis. Purpura may occur with or without septic emboli to capillaries of skin.	Normal	Normal	Normal	Normal	Capillary fragility may be increased	Normal	Normal
Allergic purpura (Henoch's and Schönlein's purpura); abnormal response of capillaries.	Bleeding results from increased capillary permeability with resultant passage of plasma and blood cells through capillary wall. Such increased permeability is probably of allergic origin (drug intoxication, food idiosyncrasies and certain infections). Purpura, joint symptoms and fever were described by Schönlein. Visceral lesions may occur, including those of bowel (Henoch's purpura). Diagnosis usually made by exclusion of other causes for purpura and by associated symptoms and signs of primary abnormality.	Normal	Normal	Normal	Normal	May be normal or may show increased capillary fragility	Normal	Normal

TABLE 1 (*Continued*).

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PROTHROMBIN CONCENTRATION	PROTHROMBIN CONSUMPTION
Hemorrhagic disease associated with *thrombocytopenia, poor clot retraction and increased capillary fragility**:								
Purpura hemorrhagica; idiopathic thrombocytopenic purpura (Werlhof's disease); thrombocytopenia with variable degrees of abnormality of capillaries.	Mechanism of bleeding in this disease is known only in part: coagulation defect is associated with deficiency of "platelet enzyme"; there is poor clot retraction, with decrease in adhesiveness, rigidity and contractility; and there is apparent failure to form platelet plug in severed vessel. The vascular defect is poorly understood. This disease occurs in children; in adults it occurs largely in young women, occasionally in men. It is of undetermined origin, may be acute or chronic and is associated with variable degrees of thrombopenia, purpura and ecchymosis. Spontaneous recovery may occur in acute adolescent cases. In chronic type, splenectomy may give symptomatic cure in about 70 per cent of cases, in spite of continuing thrombocytopenia occurring in many cases. Diagnosis requires excluding causes of "secondary" thrombocytopenia.	Usually prolonged	Normal	Poor	Decreased	Marked increase in capillary fragility	Normal	Poor
"Secondary" or "symptomatic" thrombocytopenic purpura (thrombocytopenia with variable degrees of abnormality of capillaries)	Mechanism of bleeding is the same as that in purpura hemorrhagica. It is acute or chronic hemorrhagic disease, with symptoms and signs similar to those of idiopathic thrombocytopenia, and may occur in children and adults of both sexes. Thrombocytopenia may be associated with such conditions as invasion of bone marrow (myelophthisis), aplastic marrow, irradiation, drug intoxication, as with benzol, allergic response, as possibly illustrated by "sensitivity" to organic arsenical drugs, Sedormid and sulfonamides, following thermal burns, nutritional deficiency, in pernicious anemia, and occasionally with uremia.	Usually prolonged (may show great variation)	Normal	Poor	Decreased (may show great variation)	Marked increase in capillary fragility (may show great variation)	Normal	Poor (may show great variation)
Hemorrhagic diseases associated with manifest *abnormalities of clot formation*:								
Hypoprothrombinemia Lack of prothrombin or presence of antiprothrombin substance administered, such as Dicumarol	Mechanism of bleeding is impaired blood coagulation. Hypoprothrombinemia may be associated with severe hemorrhagic disease as evidenced by purpura, ecchymoses and bleeding into any tissue. Hypoprothrombinemia may occur in such conditions as congenital absence (rare); faulty absorption of vitamin K, as in absence of bile salts and in melena neonatorum; steatorrhea or diarrhea; defective formation by diseased liver; and administration of Dicumarol and large doses of salicylates. Vitamin K, administered parenterally, usually restores prothrombin if there is adequate liver function; massive doses may be needed after Dicumarol therapy.	May be increased in severe cases	May be increased in severe cases	Normal†	Normal	Capillary fragility may be increased in severe cases	Decreased (usually only defect)	Normal
Circulating anticoagulants (heparin and other anticoagulants)	Bleeding results from inhibition of coagulation by anticoagulants circulating in blood stream in such conditions as administration of heparin and ionizing doses of irradiation probably due to heparinemia. In other cases type of anticoagulant has not been classified.	Normal	Prolonged (patient's plasma may prolong clotting time of normal plasma or whole blood)	Normal	Normal	Normal	Normal	No studies reported

*Relation between thrombocytopenia and capillary fragility is not known.

†Clotting time of whole blood *not* reliable index of degree of hypoprothrombinemia.

TABLE 1 (*Continued*).

DISEASE	COMMENTS ON MECHANISM	BLEEDING TIME	COAGULATION TIME	CLOT RETRACTION	PLATELET COUNT	TOURNIQUET TEST	PROTHROMBIN CONCENTRATION	PROTHROMBIN CONSUMPTION
Hemophilia Deficiency in blood plasma of material required for normal coagulation	Bleeding results from deficiency of plasma factor, probably thromboplastic in action. Hemophilia is sex-linked recessive hereditary disease occurring only in males and transmitted only by females. It is characterized by prolonged clotting time and marked susceptibility to hemorrhagic manifestations throughout life. Hemorrhages occur from trauma and appear "spontaneously," affecting any tissue or organ. Hemarthroses are frequent. Administration of fresh whole blood, plasma or plasma fractions results in transient reduction of coagulation time toward normal, with or without decrease in bleeding.	Initially normal, but puncture wound may subsequently bleed indefinitely	Prolonged in variable degree	Normal	Normal	Normal	Normal	Poor
Deficiency of fibrinogen; fibrinogenopenia; afibrinogenemia. Deficiency or absence of fibrinogen	Abnormal bleeding is result of impaired blood coagulation. Deficiency or absence of plasma fibrinogen occurs rarely and may be associated with hemorrhagic symptoms and signs similar to those occurring in hemophilia but without hemathroses. Absence of fibrinogen occurs as rare congenital anomaly; acquired fibrinogenopenia may be complication of severe parenchymal disease of liver, or presence of plasma fibrinolysin.	Normal	Prolonged‡	May be reduced	Normal	Normal	Normal§	Normal
Parahemophilia (Owren's disease) Deficiency of Factor V of Owren	Disease has been reported only in females but males should be equally affected. It is probably hereditary and is characterized, clinically, by epistaxis, ecchymoses following trauma, hematuria, menorrhagia and metrorrhagia. Hemarthrosis did not occur in Owren's patient. Congenital absence of factor in plasma required for conversion of prothrombin to thrombin results in prolongation of coagulation time and hemorrhagic manifestations. Addition of normal whole blood in vitro and in vivo corrects all laboratory and clinical abnormalities.	Normal	Characteristically prolonged	Normal	Normal	Normal	Normal¶	Poor

‡Coagulation of blood may be absent in afibrinogenemia; it may be quite normal until fibrinogen level is greatly reduced (levels of 50 to 75 mg. per 100 cc.).

§Prothrombin concentration is normal but cannot be determined by one-stage method since fibrinogen may be absent and must be added.

¶Prothrombin time is prolonged by use of one-stage Quick method but is normal if plasma-dilution technic is employed.

coagulation, determination of prothrombin activity and prothrombin consumption, all of which are described in detail below, and determination of fibrinolysins, determination of fibrinogen, vitamin C level of buffy coat, therapeutic trial with vitamin C and vitamin K and specific tests for circulating anticoagulants, which are discussed elsewhere.[1, 6, 7-16]

It is frequently desirable or necessary to conduct other special examinations in patients with hemorrhagic diathesis to establish the diagnosis or response to treatment of the underlying disease process.

Special Tests for Hemorrhagic Disease

A partial list of special examinations that may be indicated in patients with hemorrhagic disease includes examinations of blood for leukemia, pernicious anemia and aplastic anemia; smear or biopsy* of bone marrow for morphology and number of platelets, and megakaryocytes, signs of neoplasia, aplasia and hyperplasia; biopsy* of lymph nodes or other structures; splenectomy as a therapeutic test in idiopathic thromobcytopenia or certain cases of secondary thrombocytopenia; examinations for the presence of infections; examinations of urine for drugs (sulfonamides, barbiturates and arsenic); x-ray examination of the gastrointestinal tract for bleeding; and study of the function of the liver as related to hypoprothrombinemia.

*All surgical procedures in a patient with hemorrhagic diathesis are done after consideration of possible complications of bleeding. In hemophilia, for example, surgical intervention may be hazardous even under carefully controlled conditions.

Classification of Hemorrhagic Diseases

A brief classification of hemorrhagic diseases, based on known abnormalities and changes in certain tests for hemorrhagic diathesis, is presented in Table 1. Such a table is necessarily incomplete and oversimplified; more complete discussions of the diseases and their physiologic causes have been given elsewhere.[1-3, 6-67]

History

A complete and critical history is of first importance in the diagnosis of the cause of hemorrhagic diathesis. Often, the history alone provides adequate data on which to base a presumptive diagnosis. The history of abnormal bleeding occurring in alternate generations in male members of a family is presumptive evidence for the diagnosis of hemophilia. The history of familial bleeding that is not sex-linked suggests the possibility of "thrombasthenia." One may best obtain the *family history* by setting up a family tree on paper and, together with the patient and other members of the family, discussing and determining hemorrhagic diatheses in each member of the family as far ancestrally as is known. Often, it is necessary to question the patient and relatives to determine the onset and characteristics of bleeding. It is of importance to know the age of the patient at the *onset of bleeding*. An acute episode frequently brings the patient to the physician, but the past history will reveal many episodes of bleeding tendency reflected in such observations as frequent epistaxis, easy bruising, menorrhagia, metrorrhagia, hemarthrosis simulating arthritis, bleeding with eruption of deciduous and permanent teeth and severe hemorrhage with minor surgical procedures, such as circumcision, tonsillectomy and tooth extractions. The relation of bleeding at time of menses should be carefully investigated, since exaggeration of the normal menstrual bleeding may serve as an important index of a hemorrhagic diathesis. It is of importance to determine whether the patient has been exposed to potentially harmful drugs, chemicals or physical agents. The presence of infection, allergic symptoms or other diseases such as anemia is investigated historically in the patient. A dietary history may reveal an inadequate intake of vitamin C over a prolonged period and may thus suggest the diagnosis of scurvy.

Physical Examination

Usually, the physical signs occurring in hemorrhagic diseases do not permit a specific diagnosis to be made. The physical signs will depend on the site of hemorrhage. In *familial telangiectasia*, the lesions may be seen in the skin and mucous membranes.[24] In *purpura** petechiae may predominate in dependent portions of the body and may be associated with bleeding of the mucous membranes. Intracranial hemorrhage may be manifested by signs of hemiplegia, but there may be little evidence of hemorrhage elsewhere in the body. The follicular and perifollicular purpura of *scurvy* may be associated with massive hemorrhage into muscles and subcutaneous tissues without hemarthrosis.

In *hemophilia*, the occurrence of hemarthrosis is frequent enough to suggest the diagnosis. However, at any one time, there may be only one site of bleeding, such as hematuria, or there may be bleeding into more than one joint or into skin, muscle, mucous membranes or viscera.

The *complications of hemorrhage* may include the following: loss of large amounts of blood; pain and swelling; pressure from hematomas with obstruction of air passages and with atrophy of nerves or muscles; and deformities of joints. If hemorrhagic diathesis is a complication of another disease, the physical signs of the primary disease may be manifest, such as those of infection, anemia, leukemia, lymphoma or cancer.

Basic Examination of Blood, Urine and Stool

In the basic examination of the blood, it may be possible at the time of capillary puncture and venipuncture to detect a prolonged bleeding time or an increase in capillary fragility. Anemia may or may not be present. The stained film of blood may permit the immediate detection of thrombocytopenia, leukemia, myeloid leukocytosis or other abnormalities that may serve as diagnostic aids. There may be hematuria or blood in the stool. There may be jaundice with choluria, acholic stools or variable evidence of disease of the liver.

Measurement of Capillary Fragility

Principle

With rupture of capillaries the extravasation of blood into the skin forms a purple or purpuric spot. If there is a larger area of bleeding into the skin an ecchymotic area is formed that is dark red or blue, later changing to greenish or brown as the hemoglobin is converted, apparently, to biliverdin and bilirubin and subsequently removed.

Two terms are used to describe the susceptibility of capillaries to rupture and have resulted in some confusion. Both expressions have the same meaning, and thus it is correct to speak synonymously of *increased* capillary *fragility* or *decreased* capillary *resistance*. The ability of the capillary to withstand pressure is measured in two ways: by increase in the venous pressure by means of a blood-pressure cuff used as a tourniquet (tourniquet test); and by application of a known negative pressure to an area of the skin by the Dalldorf[68] method.

In the *Dalldorf method* a negative pressure equivalent to 200 mm. of mercury is maintained for 1

*Purpura is not a disease entity but a physical *sign*. Purpura means, literally, a purple shellfish from which a purple dye was extracted.

minute over a circular area 1 cm. in diameter on the outer side of the upper arm, and the number of petechiae produced are counted. Fewer than 10 petechiae were observed by Aggeler, Howard and Lucia[69] in 92 per cent of 64 normal subjects tested, with a range of none to more than 30. Although the Dalldorf method has certain advantages, such as reproducibility and ease of quantitative measurement, it requires specialized apparatus that is not usually available. The tourniquet test or positive-pressure method is most commonly used and is described below.

Tourniquet Test for Capillary Fragility

The forearm and hand are inspected in advance of the test for purpuric spots, nevi and hemangiomas that might be confused with petechiae produced by the test. These are marked with a ring of ink. A blood-pressure cuff is applied about the upper arm in the usual manner, and the *blood pressure accurately determined.* Although the usual procedure employs a pressure midway between systolic and diastolic pressure for five minutes, it is *recommended* that a pressure equivalent to *100 mm. of mercury* be employed for *ten minutes.* (If the patient's systolic blood pressure is 100 or less, a pressure is used that is midway between systolic and diastolic pressure.) After ten minutes the cuff is removed, and five minutes later the forearm, hand and fingers are examined on all sides for petechiae. One may devise a refinement by drawing a circle 5 cm. in diameter, located on the flexor surface of the forearm, 2.5 cm. below the antecubital fossa. The petechiae in this area are counted. It is recommended that a normal subject be examined as a control and as an aid in estimating the degree of abnormality of a positive test.

Limitations and interpretations. Normal subjects show no petechiae or a few scattered petechiae just below the margin of the cuff. In a circle 5 cm. in diameter, the upper limit of normal is approximately 10 to 15 purpuric spots (adequate data for the range of normal are not available). In positive tests, the entire forearm and hand may show myriads of petechiae that may be separate or confluent.

The result on the whole arm is *graded* in a crude manner from + to ++++ as follows: +, slight increase over normal; ++ ,many petechiae over the anterior surface of forearm; +++, multiple petechiae over the whole arm and dorsum of the hand; and ++++ confluent petechiae in all areas of the arm and dorsum of the hand. *It is emphasized that a significant increase in capillary fragility may be missed by the use of a pressure below 100 mm. of mercury for only five minutes or a pressure equivalent to 100 mm. of mercury when the systolic blood pressure is less than 100.*

The tourniquet test is primarily a measurement of the integrity of the *vascular factors* in hemostasis. The degree of positivity, however, is also a measure of the extravascular factors as well as the factors of clot formation, since blood must leave the vessel if a petechia is to be formed. Once blood escapes from the vessel lumen, factors in the surrounding tissue and within the blood itself come into play. Although an increase in capillary fragility does not permit a specific diagnosis to be made, certain facts are known.

In *scurvy*, there may be marked hemorrhagic diathesis characterized by an extreme increase in capillary fragility with formations of hematomas, apparently related to deficiency of intercellular collagen substance. There is no abnormality of the other special tests, as shown in Table 1. It is particularly noteworthy that the bleeding time is normal in scurvy and that the abnormal capillary fragility disappears in a few days after administration of vitamin C or orange juice.

In "*thrombasthenia,*" a disease or group of diseases[2] of unknown origin, the capillaries have been reported to be abnormal in shape and in contractility; there is usually an increase in capillary fragility, but the number of platelets is normal.[2] The capillary fragility may be normal or abnormal (Table 1).

In severe *thrombocytopenia* of primary or secondary origin there usually occur bleeding from mucous membranes, purpura, increased capillary fragility, prolonged bleeding time and decreased clot retraction. There is considerable evidence from Macfarlane,[2] Bedson[29] and others that the abnormality of the capillary may result from poor contraction of the capillary, but the relation to thrombocytes is not defined. There is also evidence that the site of petechial hemorrhage is the arterial end of the capillary loop.[63] Although normally the platelets aid in "plugging" breaks in the capillary, it has been shown that there is a failure of this "plugging" in thrombocytopenic states[4, 5] and that vasoconstriction of the severed and the adjacent vessels does occur. These observations do not agree with those of Macfarlane.[2] Although purpura and bleeding from mucous membranes occur in most cases of *severe thrombocytopenia,* there are well established exceptions. For example, after splenectomy there may be a prompt return to normal of the capillary fragility and bleeding time before there is a rise in platelets or during continued thrombocytopenia. In addition, there may be thrombocytopenia with normal capillary resistance and normal bleeding time.

In *allergic purpura* the tourniquet test may be extremely variable, presumably owing to abnormalities of the capillaries but of unknown mechanism. The same reservation is true of the purpura of sepsis.

Bleeding Time

Principle

The bleeding time is the period required for effective hemostasis to occur after infliction of a standardized wound of the capillary bed. Bleeding time depends primarily on extravascular and vascular factors and to a lesser degree on factors of clot formation. It is an arbitrary biologic procedure with many limitations. Two methods are used at present: the Duke[70] method and the Ivy[71] method. The former is employed most frequently.

Methods

Duke method. A stab wound 2 mm. in length and depth is made in the dependent portion of the lobe of the ear, a sharp-pointed scalpel blade, such as a Bard–Parker blade No. 11, being used. The ear is not manipulated but must be warm. At intervals of half a minute, the blood accumulated on the skin is removed by gentle touching of the drop, but *not the skin*, with a blotter or piece of filter paper. The end point of this test is failure of blood to appear on the blotting paper when the drop is touched. The normal range for this method is from two to four and a half minutes. A needle should *not* be used for the capillary puncture, since the round hole does not bleed well enough to produce a sensitive test.

Ivy method. A pressure equivalent to 40 mm. of mercury is maintained on the arm with the use of a blood-pressure cuff. A puncture wound 2 mm. in length and depth is made in a relatively avascular area of the forearm, just distal to the antecubital fossa. The escaping blood is absorbed on gauze pledgets and the bleeding time recorded to the nearest half minute. The normal range by this method has been reported[69] as 0 to six and four-tenths minutes, with a mean of three and two-tenths minutes.

Limitations and Interpretations

The difficulty of producing a standardized wound considerably limits this test as an aid in diagnosis. This limitation occurs also with the use of a mechanical lancet. Slight increases in bleeding time above the upper limit of normal always require that a series of such tests be made to control the variation in producing the wound and to determine the state of hemostasis. Under no circumstances should a needle be used for the puncture, since a significant increase in bleeding time may be missed that is readily demonstrable by a stab wound made by a scalpel blade.

An *increase in the bleeding time* does not permit a specific diagnosis to be made, nor does it signify an abnormality of a single mechanism. Prolongation of the bleeding time may be encountered in conditions in which the efficiency of the *extravascular factors of hemostasis* is decreased. Thus, in *aged persons*, prolongation of the bleeding time due to poor tissue tone and atrophy of subcutaneous tissue may be encountered. As a result of these senile changes, the hydrostatic pressure in the surrounding tissue may not rise to effective levels when bleeding from the vessel occurs. In addition, flabby and sparse subcutaneous tissue is not conducive to proper mechanical plugging of the open end of the vessel as it retracts.

Abnormalities in the bleeding time may also result from changes in the *vascular factors of hemostasis*. Thus, in states in which there is altered capillary contraction the bleeding time may be prolonged. In senility, poor vascular contraction may be a factor, in conjunction with poor tissue tone and tissue atrophy, to account for the sporadic prolonged bleeding time that is observed. In "*thrombasthenia*" there may be extremely variable increases in the bleeding time, which are considered to be due to altered capillary contraction since the number of platelets is normal.[2, 20-23, 25-27] A dogmatic conclusion that altered capillary contraction is the sole mechanism for prolongation of the bleeding time in this disease cannot be made since the platelet is of considerable importance in controlling the duration of the bleeding time. There is evidence that the platelets in "thrombasthenia" may not agglutinate normally,[72] and it is possible that they do not form a stable plug in the open end of the vessel to aid in effective hemostasis.

Abnormalities in *factors of clot formation*, such as failure of formation of the platelet plug in thrombocytopenia, may be a contributing cause of a prolonged bleeding time.[4, 5] Conversely, frank alterations in blood coagulation have little effect on the duration of the bleeding time. In *hemophilia* the bleeding time, as arbitrarily defined here, is "normal" in that bleeding stops within three minutes. This is explained on the basis that in hemophilia the initial vascular contraction is normal, and this, in conjunction with small amounts of tissue juice for partial coagulation, temporarily causes cessation of bleeding.[2] At a later time, such as an hour after the test, when vascular contraction has ceased, the stab wound may begin to "ooze" and bleed slowly and continuously, apparently owing to poor clot formation. The bleeding may continue until the wound is treated with thromboplastic material. Similarly, in *afibrinogenemia* the bleeding time is "normal" as a result of adequate initial vascular contraction and proper functioning of the extravascular factors concerned in hemostasis. As in hemophilia, oozing may occur later and continue unabated until fibrinogen is administered. A test of bleeding time in a known hemophilic patient or one with afibrinogenemia is to be *avoided* as an unnecessary *surgical* procedure. On the contrary, venipuncture with a 20-gauge needle is done whenever indicated and should *not* cause bleeding if

gentle pressure in maintained over the site for five to fifteen minutes after the puncture.

The bleeding time is normal in hemorrhagic states in which the only abnormality is increased capillary fragility. Thus, the bleeding time in *scurvy*, *allergic purpura* and *sepsis* is normal even though the tourniquet test is positive.

Platelet Count

The finding of thrombocytopenia does not permit an etiologic diagnosis to be made. The diagnosis of so-called idiopathic thrombocytopenia (purpura hemorrhagica) is made largely by the exclusion of conditions known to produce secondary thrombocytopenia. The role of thrombocytopenia in hemorrhagic diathesis can only be defined, in part, as pointed out above. Thrombocytopenia does not usually produce a prolongation of coagulation time as measured by the usual technic in glass, but definite prolongation of coagulation is easily demonstrable in glassware coated with silicone (Dri-film).[73]

The blood platelet has also been shown to be an important factor in blood coagulation as indicated by its effect on the conversion of prothrombin to thrombin,*[65] since the lower the platelet count, the poorer this conversion. In addition to the disturbed coagulation (in silicone-coated glass) in thrombocytopenia, there is always associated *poor clot retraction*.[66] The defects in coagulation (poor clot retraction, and decrease in adhesiveness, in rigidity and in contractility) may be factors, associated with the failure to form platelet plugs, that explain in part the bleeding tendency in thrombocytopenia.

Clot Retraction

Principle

Venous blood, containing all the factors necessary for coagulation and possessing no coagulation inhibitors, will clot spontaneously when placed in glass tubes. The clot when formed is usually a homogeneous suspension of red cells in plasma. Occasionally, if the red cells sediment rapidly or if coagulation is greatly prolonged, the clot will have an upper layer containing fibrin but no red cells and a lower layer of red clot. In either event, when the clot stands the fibrin contracts, expressing serum from the clot. This process is described as clot retraction or syneresis. In general, the correlation between poor clot retraction and thrombocytopenia is so close that an observed decrease in clot retraction may be a more reliable index of thrombocytopenia than the platelet count itself. As a corollary, a normal degree of clot retraction is good evidence that the platelet count is approximately 100 x 10^3/mm.^{3} or more. The relation of platelet function to clot retraction is not well understood.

*Prothrombin consumption.

Methods

Qualitative methods. Clot retraction can be measured qualitatively by inspection as follows: 2 cc. of blood is obtained by venipuncture during the coagulation test, as described below. The tube is placed in a water bath at 37.5°C. and observed after half an hour and one, two, four and twenty-four hours for signs of retraction — namely, the separation of the clot with expression of serum. The clot may stick to the wall of the tube and require gentle separation if retraction has not occurred within an hour. This is done by gentle rimming of the top of the clot with a platinum wire or wooden applicator.

Semiquantitative method. Fluid volume of the clot. A semiquantitative method has been described by Macfarlane[74] and modified slightly by Aggeler, Lucia and Hamlin[75] and others.[76, 77] In this method 5 cc. of venous blood is introduced into a 15-cc. graduated centrifuge tube. A cork fitted with a copper wire bent in the form of a hook is adjusted so that the hook is immersed in the upper layers of the blood. The tube is placed in a water bath at 37.5°C., and the coagulation time noted. One hour after coagulation the total volume (T) of the specimen is recorded and the retracted clot is removed by means of the hook. The residual volume of serum (S) is recorded, and the volume occupied by the clot (C) is taken to be T − S. The hematocrit is determined, in the usual manner on another portion of the blood sample, and the total corpuscular volume percentage (PCV) of formed elements is read, including the layers of white cells and of platelets. To calculate the fluid volume FV *occluded within the clot*, in percentage, the following expression is used: FV (percentage) = [(C/T)x100] − PCV. The normal range is reported as 6 to 20 per cent,[69] with a mean of 8 per cent.

Limitations and Interpretations

It is known that platelets are directly concerned with clot retraction so that good clot retraction is usually associated with normal platelet counts. However, there are various degrees of clot retraction as evidenced by moderate retraction of the clot with platelet counts of 35,000 to 40,000.[66] Other factors may influence the appearance of the clot in retraction. A reduction in fibrinogen results in the formation of a small clot that gives the false impression of normal clot retraction. Similarly, a reduction of erythrocytes, as in anemia, gives a false impression of normal clot retraction. Conversely, in polycythemia there appears to be poor clot retraction as shown by the qualitative method since the clot is large and the serum small in volume. By the use of the semiquantitative method, the volume percentage of entrapped serum is found

to be normal or average in polycythemia. A case of hyperglobulinemia has been observed in which the fluid volume was greatly increased even though the level of platelets and amount of fibrinogen were normal.[73] Thus, clot retraction may be affected not only by platelets but also by decreased fibrinogen, by the number of red blood cells and by elevated plasma proteins.

For the *qualitative method*, clot retraction occurs normally in an hour, forming a small, firm, red elastic mass. In abnormal conditions clot retraction may not occur at all in twenty-four hours, or there may be variable degrees of retraction.

Classically in *thrombocytopenia*, with a platelet count below 100 x 10^3/mm.^{3}, there is decreased clot retraction that is roughly proportional to the platelet count. In the semiquantitative method there may be no clot retraction, so that 100 per cent of the fluid volume is retained in the clot (no serum is expressed).

In "*thrombasthenia*" the platelet count is usually normal, but the clot retraction is frequently poor, suggesting abnormal function of the platelets.

In certain cases, as in medical and surgical shock, a so-called fibrinolysin,[78] which may obscure clot retraction by actual dissolution of the clot, develops.

Clot retraction is normal in the remaining hemorrhagic diseases (Table 1).

Measurement of Coagulation Time of Venous Blood in Glass Tubes — Clotting Time

Theory of Blood Coagulation

Many of the factors concerned in clot formation are as yet poorly understood. Until recently the following fundamental equations of blood coagulation had remained unchanged:

$$\text{Prothrombin} + \text{Calcium} + \text{Thromboplastin} \rightarrow \text{Thrombin}$$
$$\text{Thrombin} + \text{Fibrinogen} \rightarrow \text{Fibrin}$$

This relatively simple schema was proposed by Morawitz[18] in 1905, and it is recommended that it be used as a framework into which new factors can be fitted.

"Prothrombin accelerators" of plasma and serum. Almost simultaneously, from four different laboratories, there have recently appeared descriptions of a substance in plasma that is concerned with the speed of formation of thrombin from prothrombin. In Norway, Owren[19] has designated the substance "Factor V"; in Australia it was called "accelerator substance"[46]; one group in the United States has designated it "plasma accelerator globulin"[51]; another has called it "labile factor."[56] These various terms have led to confusion, and it is still uncertain whether they are designations of the same substance; for clarity in writing, however, they may be grouped into a single term, "prothrombin accelerators" of plasma. In addition to these "prothrombin accelerators" of plasma, three "prothrombin accelerators" of serum have been described. Owren[19] uses the term Factor VI; Ware and Seegers[61] speak of serum accelerator globulin; and Alexander[64] terms his substance serum prothrombin conversion accelerator (SPCA). Again, it may be that these three terms designate the same substance, although conclusive evidence of this is lacking. Also, it is likely that the "prothrombin accelerators" of serum are derived from the "prothrombin accelerators" of plasma, much as thrombin of serum is elaborated from prothrombin of plasma. The serum "prothrombin accelerators" are considered to be the active substances accelerating the conversion of prothrombin into thrombin, whereas the plasma "prothrombin accelerators" are relatively inert.[61]

There is little doubt that these "prothrombin accelerators" exist, since deficiencies of these components have been described as parahemophilia by Owren[53] and plasma accelerator globulin deficiency by Seegers and Craddock.[59] Although a clinical deficiency of labile factor has not been described as such, Quick and Stefanini[56] have suggested that the case described by Rhoads and Fitz-Hugh[57] probably represented such a deficiency.

Platelets in conversion of prothrombin to thrombin. It has been shown by Quick[65] and confirmed[60] that platelets are concerned with the total conversion of prothrombin to thrombin, and to a lesser degree with the speed of this reaction.[60] It has been demonstrated that the thromboplastin in platelets is not responsible for this activity,[60, 65] which has been described by Quick as "platelet enzyme" or thromboplastinogenase. It is Quick's concept that platelets are necessary for the activation (by an enzyme) of thromboplastinogen to thromboplastin, which in turn, in the presence of calcium, will convert (stoichiometrically) prothrombin to thrombin.[50]

Hypothesis of blood coagulation. To build these new factors into the framework of Morawitz is as yet a theoretical and controversial problem. By a combination of the theories of blood coagulation of Quick[66] and Ware et al.[60] it is possible to make a *working hypothesis* for the location of all components.

It has been shown[61] that the plasma "prothrombin accelerators" have essentially no effect on the yield of thrombin produced from a mixture of *purified* prothrombin, thromboplastin and calcium. It is established that the *serum* "prothrombin accelerators" cause a large evolution of thrombin in such a mixture.[19, 60, 64] Therefore, it becomes necessary to show graphically the conversion of the "prothrombin acclerators" of plasma to those of the serum type. Although the mechanism for such conversion has not been clearly shown, it may be,

as suggested by Ware and Seegers,[61] that thrombin plays a part in this reaction as follows:

Prothrombin + Thromboplastin + Calcium → Thrombin
Thrombin (?) + Plasma "prothrombin accelerators" → Serum "prothrombin accelerators"
Prothrombin + Serum "prothrombin accelerators" → Thrombin
Thrombin + Fibrinogen → Fibrin

Since Quick[66] has shown *platelets* to be important in this reaction, it is possible to eliminate the one weak point of the foregoing theory — namely, that purified prothrombin, tissue thromboplastin and calcium form little or no thrombin.[19, 61] With the "platelet enzyme" activating plasma thromboplastinogen, there results augmentation of thrombin formation as follows:

"Platelet enzyme" + Thromboplastinogen → Thromboplastin
Prothrombin + Thromboplastin + Calcium → Thrombin

The next step then involves conversion of the plasma "prothrombin accelerators" to the active serum "prothrombin accelerators" by thrombin. Thus, the theoretical steps in the coagulation of blood can be combined into a *working hypothesis*, involving the following five steps:

"Platelet enzyme" + Thromboplastinogen → Thromboplastin
Thromboplastin + Prothrombin + Calcium → Thrombin
Plasma "prothrombin accelerators" + Thrombin (?) → Serum "prothrombin accelerators"
Prothrombin + Serum "prothrombin accelerators" → Thrombin
Thrombin + Fibrinogen → Fibrin

With this concept one can endeavor to interpret abnormalities in the various laboratory tests that utilize the coagulation of blood or plasma as an end point.

Coagulation Time of Venous Blood

Principle. When unaltered venous blood, obtained by a nontraumatic venipuncture, is introduced into glass tubes the time required for clotting to occur is called the coagulation time or clotting time. This is a highly arbitrary biologic procedure since the glass surface and many other factors affect the coagulation time significantly. For example, normal blood collected in tubes made of a plastic, or tubes coated with paraffin or nonwetting agents such as silicone, requires a significantly longer time to clot (thirty to sixty minutes) than in glass tubes (six to twelve minutes). The temperature of shed blood profoundly affects the clotting time, as evidenced by the extreme prolongation (one to four hours) at a temperature of 3°C. as opposed to the relatively rapid clotting (six to twelve minutes) occurring at body temperature. Technically, the modified[8] Lee–White method for measurement of blood coagulation time is probably as reliable a procedure as is available currently. It should be remembered, however, that coagulation times obtained by this method are purely relative, and that the method is of value primarily as a screening procedure in an effort to determine plasma coagulation defects and anticoagulant activity. *The method of measurement of the coagulation time by the use of capillary blood drawn into a capillary tube is so unreliable as to be valueless; it should not be used.*

Method (modified Lee–White method). A sterile 5-cc. syringe and sterile needle are rinsed twice with sterile physiologic saline solution, and all the solution is expelled. A venipuncture is performed with the least possible stasis and trauma. The tourniquet is applied just before the venipuncture is made. Traction on the plunger of the syringe—if used at all— should be gentle, to prevent agitation of the blood and to avoid the entry of air bubbles into the syringe as the sample is drawn. If the vein is not entered on the first attempt, the needle and syringe should be discarded,* and another sterile syringe and needle, rinsed twice with sterile saline solution, employed. A sample of 5 cc. of blood is obtained, the needle is removed from the syringe, and 2-cc. samples of blood are placed in each of two chemically clean test tubes (13 by 100 mm.) that have been previously rinsed twice with physiologic saline solution. The blood should be made to run down the side of the tube *gently* to avoid agitation. The remaining 1 cc. of blood in the syringe is discarded since it contains unavoidable traces of tissue juices.* The two tubes are placed in a water bath at 37.5°C., and at intervals of approximately a minute one of the tubes is observed for clotting by removal from the bath and gentle tilting. The end point of coagulation is reached when the tube can be inverted without loss of contents. When this occurs for the first tube, the second is observed in a similar manner, until coagulation occurs in it. The beginning of the test is the time when blood first enters the syringe. The average time, in minutes, required for blood to clot in the two tubes is reported as the coagulation or clotting time. If there is a difference of more than five minutes between the coagulation times of the two tubes, the longer time is reported. This is commonly found in hemophilia.

Limitations and interpretations. The normal range (100 subjects) is from four to twelve minutes, with a mean of seven and seven-tenths minutes and a standard deviation of one and seven-tenths minutes.[39] Most errors in technic will tend to *shorten* the coagulation time; such errors include

*The tissue juices contaminating the needle and syringe from an unsuccessful venipuncture will decrease the coagulation time.

introduction of tissue fluid from a traumatic venipuncture, agitation of the blood by rapid passage through the needle, introduction of air bubbles or traumatic transfer of blood to the test tubes and unclean or rough glassware. *Prolongation* of the coagulation time may occur as a result of the following variations in technic: unduly low or high pH, unduly low or high temperatures and the use of plastic tubes or tubes coated with paraffin or nonwettable plastics (silicone-Dri-film). In view of these facts it is quite important to carry out the test at controlled temperature, pH, and calcium concentration and with technics that avoid trauma in the venipuncture, the introduction of air bubbles and unduly rough treatment of the blood obtained. The time for coagulation to occur is a purely relative test and does *not* indicate that complete coagulation has occurred for the whole column of blood. It is simply a measure of the time required for the formation of fibrin at the air interface in quantity sufficient to support the column of blood when the tube is inverted.

The coagulation time of whole blood is prolonged notably in *hemophilia* and after administration of *heparin*, varying from fifteen minutes to several hours. In general, the degree of elevation of the coagulation time is a function of the severity of the disease in hemophilia and of the effect of heparinemia. On the other hand, it has been noted that hemophilic patients with greatly prolonged coagulation times may have fewer hemorrhagic episodes than others with only slight prolongation of the coagulation time. The coagulation time of blood of a given hemophilic patient remains remarkably constant except when altered therapeutically.

In severe cases of *hypoprothrombinemia*, the coagulation time is also prolonged, but this test is unreliable as an index of prothrombin deficiency, since an increase in coagulation time is a late manifestation and indicates an extremely low and dangerous level of prothrombin, 5 per cent or less.[44] Only small amounts of prothrombin are necessary for the formation of thrombin and the subsequent fibrin formation that results in visible coagulation of blood. Accordingly, the coagulation time cannot be used with safety in following the course of hypoprothrombinemia resulting from Dicumarol therapy.

Prolongation of coagulation time is observed in *fibrinogenopenia* and completely incoagulable blood is encountered in absolute *afibrinogenemia*, whether congenital or acquired. The latter may be due to large amounts of fibrinolysin, as in shock.

Prolonged coagulation time is also encountered in *parahemophilia*[53] (Owren's disease), being due, in this instance, to a deficiency of the so-called "Factor V" of Owren.

The finding of prolongation of the clotting time is nonspecific information since it does not of itself indicate the presence of hemophilia, the absence of fibrinogen, a deficiency of a "prothrombin accelerator" or the effect of heparinemia. As mentioned above, the coagulation time in hemophilia may be restored toward normal after treatment at a time when the patient is showing active hemorrhage.

If the test is carried out in glass tubes, a *decrease in coagulation time* below six minutes has no reliable clinical value as a measure of increased coagulability of blood, such as may occur in certain diseases with abnormal tendency to thrombosis. Strictly, the coagulation time should be used only in relation to plasma coagulation defects and coagulation inhibitors such as heparin.

(*To be concluded*)

References

1. Quick, A. J. *The Hemorrhagic Diseases and the Physiology of Hemostasis.* 340 pp. Baltimore: Charles C Thomas, 1942.
2. Macfarlane, R. G. Critical review: mechanism of haemostasis. *Quart. J. Med.* **10**:1-29, 1941.
3. Tocantins, L. M. Mechanism of hemostasis. *Ann. Surg.* **125**:292-310, 1947.
4. Zucker, M. B. Platelet agglutination and vasoconstriction as factors in spontaneous hemostasis in normal, thrombocytopenic, heparinized and hypoprothrombinemic rats. *Am. J. Physiol.* **148**:275-288, 1947.
5. Zucker, H. D. Platelet thrombosis in human hemostasis. *Blood* **4**:631-645, 1949.
6. Wintrobe, M. M. *Clinical Hematology.* Second edition. 862 pp. Philadelphia: Lea & Febiger, 1946.
7. Lewis, J. H., Tagnon, H. J., Davidson, C. S., Minot, G. R., and Taylor, F. H. L. Relation of certain fractions of plasma globulins to coagulation defect in hemophilia. *Blood* **1**:166-172, 1946.
8. Patek, A. J., Jr., and Stetson, R. P. Hemophilia. I. Abnormal coagulation of blood and its relation to blood platelets. *J. Clin. Investigation* **15**:531-542, 1936.
9. Patek, A. J., Jr., and Taylor, F. H. L. Hemophilia. II. Some properties of substance obtained from normal human plasma effective in accelerating coagulation of hemophilic blood. *J. Clin. Investigation* **16**:113-124, 1937.
10. Tagnon, H. J., Davidson, C. S., and Taylor, F. H. L. Coagulation defect in hemophilia: comparison of proteolytic activity of chloroform preparations of hemophilic and normal human plasma. *J. Clin. Investigation* **22**:127-129, 1943.
11. Allen, J. G., and Jacobson, L. O. Hyperheparinemia: cause of hemorrhagic syndrome associated with total body exposure to ionizing radiation. *Science* **105**:388, 1947.
12. Allen, J. G., Bogardus, G., Jacobson, L. O., and Spurr, C. L. Some observations on bleeding tendency in thrombocytopenic purpura. *Ann. Int. Med.* **27**:382-395, 1947.
13. Craddock, C. G., Jr., and Lawrence, J. S. Hemophilia: report of mechanism of development and action of anticoagulant in two cases. *Blood* **2**:505-518, 1947.
14. Dieter, D. G., Spooner, M., and Pohle, F. J. Studies on undetermined circulating anticoagulant. Case report and laboratory findings. *Blood* **4**:120-129, 1949.
15. Frommeyer, W. B., Epstein, R. D., and Taylor, F. H. L. Unpublished data.
16. Lozner, E. L., Jolliffe, L. S., and Taylor, F. H. L. Hemorrhagic diathesis with prolonged coagulation time associated with circulating anticoagulant. *Am. J. M. Sc.* **199**:318-327, 1940.
17. Eagle, H. Recent advances in blood coagulation problem. *Medicine* **16**:95-138, 1937.
18. Morawitz, P. Die Chemie der Bluterinnung. *Ergebn. d. Physiol.* **4**: 307-422, 1905.
19. Owren, P. A. Coagulation of blood: investigations on new clotting factor. *Acta med. Scandinav.* Supp. 194, 1947. Pp. 1-327.
20. Cronkite, E. P., and Lozner, E. L. Hereditary hemorrhagic thrombasthenia with severe post-hemorrhoidectomy hemorrhage. *U. S. Nav. M. Bull.* **42**:161-164, 1944.
21. Estren, S., Sanchez Medal, L., and Dameshek, W. Pseudohemophilia. *Blood* **1**:504-533, 1946.
22. Geiger, A. J., and Evans, A. G. Atypical hereditary hemorrhagic syndromes. *New Internat. Clin.* **2**:135-157, 1938.
23. Glanzmann, E. Hereditäre hämorrhagische Thrombasthenie. Ein Beitrag zur Pathologie der Blutplättchen. *Jahrb. f. Kinderh.* **88**: 1 and 113-141, 1918.
24. Goldstein, H. I. Goldstein's heredofamilial angiomatosis (telangiectasia) with recurring familial hemorrhages (Rendu-Osler Weber's disease). *Arch. Int. Med.* **48**:836-865, 1931.
25. Halliwell, H. L., and Brigham, L. Pseudohemophilia. *Ann. Int. Med.* **29**:803-810, 1948.
26. Hewlett, J. S., and Haden, R. L. Hereditary pseudohemophilia: report of four cases. *Cleveland Clin. Quart.* **15**:118-124, 1948.

27. von Willebrand, E. A. Über hereditäre Pseudohämophilie. *Acta med. Scandinav.* **76**:521-550, 1931.
28. Aggeler, P. M., Lindsay, S., and Lucia, S. P. Studies on coagulation defect in case of thrombocytopenic purpura complicated by thrombosis. *Am. J. Path.* **22**:1181-1203, 1946.
29. Bedson, S. P., Blood-platelet anti-serum, its specificity and rôle in experimental production of purpura. *J. Path. & Bact.* **25**:94-104, 1922.
30. Dameshek, W., and Miller, E. B. Megakaryocytes in idiopathic thrombocytopenic purpura, form of hypersplenism. *Blood* **1**: 27-51, 1946.
31. Falconer, E. H., Epstein, N. N., and Mills, E. S. Purpura hemorrhagica due to arsphenamines: sensitivity in patients as influenced by vitamin C therapy. *Arch. Int. Med.* **66**:319-338, 1940.
32. Falconer, E. H., and Schumacher, I. C. Purpura hemorrhagica due to ingestion of Sedormid (allylisopropylacetylcarbamide): experimental observations and report of case. *Arch. Int. Med.* **65**:122-137, 1940.
33. Fitzgerald, P. J., Auerbach, O., and Frame, E. Thrombocytic acro-angiothrombosis (platelet thrombosis of capillaries, arterioles, and venules). *Blood* **2**:519-541, 1947.
34. Rappoport, A. E., Nixon, C. E., and Barker, W. A. Fatal secondary, toxic thrombocytopenic purpura due to sodium salicylate: report of case. *J. Lab. & Clin. Med.* **30**:916-927, 1945.
35. Tocantins, L. M. Experimental thrombocytopenic purpura: cytological and physical changes in blood. *Ann. Int. Med.* **9**:838-849, 1936.
36. Davidson, C. S., Epstein, R. D., Miller, G. F., and Taylor, F. H. L. Hemophilia. Clinical study of forty patients. *Blood* **4**:97-119, 1949.
37. Howell, W. H. Hemophilia. *Bull. New York Acad. Med.* **15**:3-26, 1939.
38. Aggeler, P. M., Howard, J., Lucia, S. P., Clark, W., and Astaff, A. Standardization of Quick prothrombin test, with reference to statistical significance of variations in prothrombin concentration with use of stable thromboplastin of high potency. *Blood* **1**: 220-233, 1946.
39. Alexander, B. Unpublished data.
40. Alexander, B., and deVries, A. Human prothrombin: quantitative studies on plasma labile factor and restorative effects of normal, hypofibrinogenic and hemophilic plasma on prothrombin of stored plasma. *J. Clin. Investigation* **28**:24-31, 1949.
41. *Idem.* Studies on hemophilia. V. Coagulation defect in hemophilia with particular reference to conversion of prothrombin to thrombin and evaluation of prothrombin conversion accelerator. *Blood* **4**: 752-758, 1949.
42. Bollman, J. L., Butt, H. R., and Snell, A. M. Influence of liver on utilization of vitamin K. *J. A. M. A.* **115**:1087-1091, 1940.
43. Brinkhous, K. M. Plasma prothrombin: Vitamin K. *Medicine* **19**: 329-416, 1940.
44. Davidson, C. S., and MacDonald, H. Critical study of action of 3-3′methylenebis (4-hydroxycoumarin) (Dicoumarin). *Am. J. M. Sc.* **205**:24-33, 1943.
45. deVries, A., Alexander, B., and Goldstein, R. Factor in serum which accelerates conversion of prothrombin. I. Its determination and some physiologic and biochemical properties. *Blood* **4**;247-258, 1949.
46. Fantl, P., and Nance, M. Acceleration of thrombin formation by plasma component. *Nature*, London **158**:708, 1946.
47. Ferguson, J. H., and Lewis, J. H. "Accelerator globulin" and "anti-hemophilic globulin" in thrombin formation from *aged* prothrombin and in hemophilic blood. *Proc. Soc. Exper. Biol. & Med.* **67**:228-231, 1948.
48. Frommeyer, W. B. Determination of prothrombin by dilution method: stability and activity of human and bovine prothrombin-free plasma. *J Lab. & Clin. Med.* (in press).
49. Link, K. P. Anticoagulant from spoiled sweet clover hay. *Harvey Lect.* (1943-1944) **39**:162-216, 1944.
50. Mertz, E. T., Seegers, W. H., and Smith, H. P. Prothrombin, thromboplastin, and thrombin: quantitative interrelationships. *Proc. Soc. Exper. Biol. & Med.* **42**:604-609, 1939.
51. Murphy, R. C., Ware, A. G., and Seegers, W. H. Plasma ac-globulin activity. *Am. J. Physiol.* **151**:338-341, 1947.
52. *Idem.* Stability of serum ac-globulin. *Proc. Soc. Exper. Biol. & Med.* **69**:216, 1948.
53. Owren, P. A. Parahaemophilia: haemorrhagic diathesis due to absence of previously unknown clotting factor. *Lancet* **1**:446-448, 1947.
54. Quick, A. J. Congenital hypoprothrombinaemia and pseudo-hypoprothrombinaemia. *Lancet* **2**:379-382, 1947.
55. Quick, A. J., and Grossman, A. M. Nature of hemorrhagic disease of newborn: delayed restoration of prothrombin level. *Am. J. M. Sc.* **199**:1-9, 1940.
56. Quick, A. J., and Stefanini, M. Concentration of labile factor of prothrombin complex in human, dog, and rabbit blood; its significance in determination of prothrombin activity. *J. Lab. & Clin. Med.* **33**:819-826, 1948.
57. Rhoads, J. E., and Fitz-Hugh, T., Jr. Idiopathic hypoprothrombinemia — apparently unrecorded condition. *Am. J. M. Sc.* **202**: 662-670, 1941.
58. Rosenfield, R. E., and Tuft, H. S. Estimation of prothrombin level from prothrombin time. *Am. J. Clin. Path.* **17**:405-412, 1947.
59. Seegers, W. H., and Craddock, C. G., Jr. Personal communication.
60. Ware, A. G., Fahey, J. L., and Seegers, W. H. Platelet extracts, fibrin formation and interaction of purified prothrombin and thromboplastin. *Am. J. Physiol.* **154**:140-147, 1948.
61. Ware, A. G., and Seegers, W. H. Serum ac-globulin: formation from plasma ac-globulin; role in blood coagulation; partial purification; properties; and quantitative determination. *Am. J. Physiol.* **152**: 567-576, 1948.
62. Warner, E. D., Brinkhous, K. M., and Smith, H. P. Quantitative study on blood clotting: prothrombin fluctuations under experimental conditions. *Am. J. Physiol.* **114**:667-675, 1936.
63. Humble, J. G. Mechanism of petechial hemorrhage formation. *Blood* **4**:69-75, 1949.
64. Alexander, B., and deVries, A. Studies on factor in serum which accelerates conversion of prothrombin to thrombin. III. Its relation to coagulation defect in thrombocytopenic blood. *Blood* **4**:747-751, 1949.
65. Quick, A. J. Studies on enigma of hemostatic dysfunction of hemophilia. *Am. J. M. Sc.* **214**:272-280, 1947.
66. Quick, A. J., Shanberge, J. N., and Stefanini, M. Role of platelets in coagulation of blood. *Am. J. M. Sc.* **217**:198-205, 1949.
67. Macfarlane, R. G., and Biggs, R. Fibrinolysis. Its mechanism and significance. *Blood* **3**:1167-1187, 1948.
68. Dalldorf, G. Sensitive test for subclinical scurvy in man. *Am. J. Dis. Child.* **46**:794-802, 1933.
69. Aggeler, P. M., Howard, J., and Lucia, S. P. Platelet counts and platelet function. *Blood* **1**:472-496, 1946.
70. Duke, W. W. Relation of blood platelets to hemorrhagic disease: description of method for determining bleeding time and coagulation time and report of three cases of hemorrhagic disease relieved by transfusion. *J. A. M. A.* **14**:1185-1192, 1910.
71. Ivy, A. C., Shapiro, P. E., and Melnick, P. Bleeding tendency in jaundice. *Surg., Gynec. & Obst.* **60**:781-784, 1935.
72. Jürgens, R. Die erblichen Thrombopathien. *Ergebn. d. inn. med. u. Kinderh.* **53**:795-826, 1937.
73. Frommeyer, W. B. Unpublished data.
74. Macfarlane, R. G. Simple method for measuring clot-retraction. *Lancet* **1**:1199-1201, 1939.
75. Aggeler, P. M., Lucia, S. P., and Hamlin, L. M. Blood clot retraction. I. Measurement of extracorpuscular volume of clot. *J. Lab. & Clin. Med.* **28**:89-97, 1942.
76. Lucia, S. P., Aggeler, P. M., and Hamlin, L. H. Blood clot retraction. II. Significance of extracorpuscular volume of clot and its clinical application. *Am. J. M. Sc.* **204**:507-516, 1942.
77. Tocantins, L. M. Platelets and spontaneous syneresis of blood clots. *Am. J. Physiol.* **110**:278-286, 1934.
78. Tagnon, H. J., Levenson, S. M., Davidson, C. S., and Taylor, F. H. L. Occurrence of fibrinolysis in shock, with observations on prothrombin time and plasma fibrinogen during hemorrhagic shock. *Am. J. M. Sc.* **211**:88-96, 1946.

CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

TRACY B. MALLORY, M.D., *Editor*

BENJAMIN CASTLEMAN, M.D., *Associate Editor*

EDITH E. PARRIS, *Assistant Editor*

CASE 35441

PRESENTATION OF CASE

A seventy-two-year-old Finnish-born, married steel worker entered the hospital with a chief complaint of "severe" shortness of breath.

Two years before entry the patient was told that he had an "irregular" heart but successfully discharged his duties as a steel worker until eleven months before entry, when he tripped and fell 20 feet while on the job and injured the left seventh, eighth and ninth ribs anteriorly and his left hand. Radiograms of the chest were reported as not remarkable except for the rib fractures. After spending twelve days in two other hospitals he returned home but not to his job. The patient dated the beginning of his dyspnea as shortly after this accident. About nine months before admission vague precordial pain, described by the patient as "constriction" and "congestion," appeared especially after exertion but frequently at night. This discomfort lasted usually about five minutes but occasionally much longer and did not always disappear with rest. No radiation of pain to the shoulders or arms was ever present. The dyspnea temporarily improved three and a half months before entry so that he was content to take care of his flock of turkeys and do other small jobs. However, his dyspnea recurred in the next month, and he was denied even these minor pleasures, being unable to walk short distances without excessive fatigue. A slight cough productive of small amounts of whitish sputum appeared. About five weeks before entry he developed hay fever (which he had experienced in the past) and noted more difficulty sleeping at night, requiring two pillows to sleep comfortably. One month before entry he noted an increase in his anorexia, which he believed had been present since his accident. He further noted a weight loss of about 20 pounds in the last five or six months.

He visited the Medical Clinic of the Out Patient Department one month before admission, and an additional history was obtained of exposure to tuberculosis; a daughter had the disease several years previously and a sister-in-law was similarly afflicted thirty years before. Examination at this time revealed a blood pressure of 150 systolic, 90 diastolic, a pulse rate of 80, with 8 to 10 skipped beats at the wrist per minute, and a Grade II apical systolic murmur and auricular fibrillation; no definite cardiac enlargement was noted. The temperature was 97°F., and the respiratory rate 20. The lungs were resonant, and basilar rales cleared on coughing. A firm,

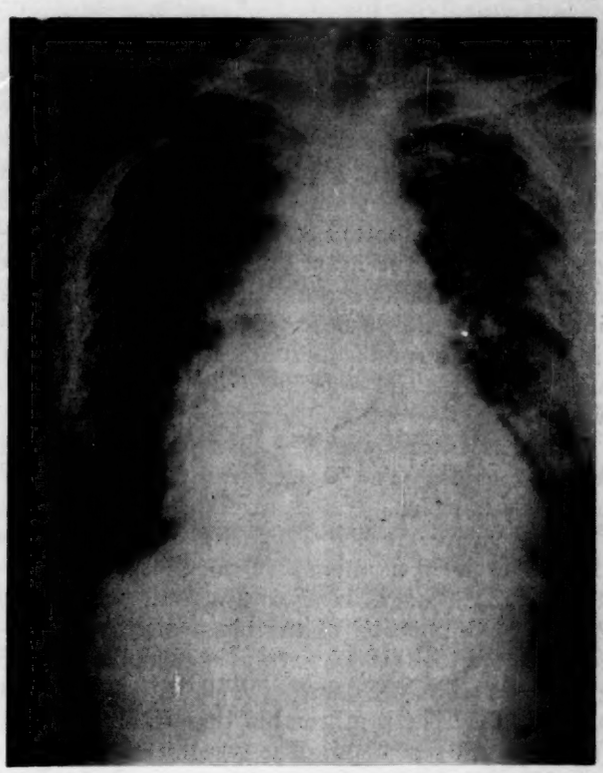

FIGURE 1.

nontender right supraclavicular node (1.5 cm. in diameter) was noted. Abdominal and rectal examinations were not remarkable. A blood Hinton test was negative. Urinalysis was negative. Radiograms of the chest revealed an enlarged heart (Fig. 1) with a cardiothoracic ratio of 18:25, the enlargement appearing predominantly in the region of the left ventricle. The lung fields exhibited extensive, diffuse, linear and mottled densities, particularly in the middle and lower portions. The hilar vascular shadows were poorly seen but appeared somewhat enlarged. The patient was digitalized and given nitroglycerin.

Two weeks before entry he was again seen in the Medical Clinic, at which time his blood pressure was 130 systolic, 80 diastolic, and the pulse and breath

sounds were essentially unchanged. Very shortly thereafter the dyspnea rapidly increased, three or four pillows being required at night. Five days preceding entry the dyspnea became so severe that virtually no sleep was obtainable, the patient having to sit in a chair or upright in bed to facilitate easy breathing. The next day he developed ankle edema, which gradually increased.

Physical examination on admission revealed a well developed, well nourished, somewhat apprehensive but co-operative man with extraordinary dyspnea, coughing frequently and usually swallowing the sputum. Cyanosis of the lips, fingers and mucous membranes was present. Bilateral distention of the neck veins, slightly more marked on the left, was evident in the upright position. A few small, hard nodes were present in each supraclavicular region. The chest was moderately emphysematous, and dullness was present on the right posteriorly and in the axilla to the angle of the scapula, with decreased breath and spoken voice sounds; dry rales were present in the right chest above the area of dullness, but no rales were noted on the left. The notable cardiac signs were a maximal impulse of the heart 11 cm. to the left of the midsternal line in the lower fifth interspace, auricular fibrillation with a 10-beat pulse deficit, some occasional bigeminy, and a short apical systolic murmur. Moderate ankle and slight to moderate sacral edema was present.

The temperature was 97°F., the pulse 80, and the respirations 32. The blood pressure was 135 systolic, 90 diastolic.

Investigative studies revealed a circulation time (Decholin) of 50 seconds, a venous pressure equivalent to 222 mm. of water and a vital capacity of 900 cc. Examination of the blood disclosed a red-cell count of 5,100,000, with a hemoglobin of 14.5 gm., and a white-cell count of 9550, with 80 per cent neutrophils. The prothrombin time was 19 seconds (normal, 15 seconds). The nonprotein nitrogen was 28 mg., the blood sugar 96 mg., and the total protein 5.9 gm., per 100 cc., and the sodium 127.8 milliequiv., the chloride 92 milliequiv. and the carbon dioxide 22.7 milliequiv. per liter; the alkaline phosphatase was 4.6 units per 100 cc. The phenolsulfonephthalein test showed 62 per cent excretion of the dye, and the bromsulfalein test 64 per cent retention of the dye. The gastric acidity was in the normal range. Sputum smears were negative for acid-fast organisms and abnormal cells. Two separate gastric washings were positive for tumor cells and gave a ++++ guaiac reaction. The stools were consistently guaiac positive. Urinalysis was not remarkable; the urinary sodium chloride was 1 or 2 gm. per 24 hours. An electrocardiogram revealed auricular fibrillation, low voltage, sagging ST segments in Lead 1 and 2 and AVL and V_6, and inverted T waves in Lead 1 and 2 and AVL and V_4 and V_6.

Radiographic studies demonstrated very little change in the chest since the previous examination. A roentgenogram of the abdomen was marred by the dyspnea, the only discernible visceral outline being that of the liver, which was at the upper limits of normal; some air was present in the large bowel, and little or none in the small bowel. A gastrointestinal series was attempted but was incomplete and unsatisfactory because of the patient's extreme illness; however, the midportion of the posterior wall of the stomach appeared to be rather straight, and the duodenal bulb was deformed. X-ray films of the bones were normal.

The patient was placed on a cardiac regime, including digitoxin, ammonium chloride, Sodium Amytal, Mercuhydrin, a diet moderately low in sodium, and other supportive therapy. Despite these measures he continued to be critically ill and died on the sixth hospital day.

Differential Diagnosis

Dr. Allen G. Brailey*: It is hard to know what to take up first when one is confronted with this welter of signs and symptoms. We might begin by seeing the x-ray films.

Dr. James J. McCort: On the initial chest examination the strand-like and coarse and finely nodular increase in density in both lungs is well seen. These changes extend outward from the hilus to the periphery and involve the greater portion of both lungs. There is no fluid in either costophrenic sinus. The heart is markedly enlarged to the left and right (Fig. 1), and there is definite fullness anteriorly, suggesting right ventricular enlargement. A widening of the hilar shadows is seen, suggesting dilatation of the main pulmonary arteries. A film of the chest made one month after the first examination shows very little change except possibly a small amount of fluid in the right costophrenic sinus.

Examination of the gastrointestinal tract was unsatisfactory because of the severe dyspnea. The esophagus was normal. On one film a flattening of the posterior wall of the stomach near the lesser curvature is demonstrated. There is also a slight constriction of the duodenal cap and a small diverticulum of the second portion of the duodenum.

Dr. Edward F. Bland: Are the bones all right?

Dr. McCort: The skull and long bones were not abnormal.

Dr. Brailey: What about the possibility of a pathologic fracture two years before admission?

Dr. McCort: I can see no evidence of it.

Dr. Brailey: There is enlargement of the heart. Is it mostly right or left ventricle? The protocol says "left."

Dr. McCort: It is impossible to determine which ventricle is larger. There is definite right ventricular enlargement.

*Assistant physician, Massachusetts General Hospital.

DR. BRAILEY: Could the shadows in the lung be tuberculosis?

DR. MCCORT: There is no evidence of cavitation or calcification to indicate tuberculosis.

DR. BRAILEY: Do you think the shadows are due to embolization?

DR. MCCORT: Multiple small emboli could produce similar nodular densities, but there are strand-like densities in addition to nodules.

DR. BRAILEY: Have you ever seen metastatic carcinoma present this kind of picture?

DR. MCCORT: A small percentage of metastatic carcinomas show a lymphatic permeation that is compatible with this picture.

DR. BRAILEY: There is no interference with the bronchi as far as you can see—no obstruction?

DR. MCCORT: There is no narrowing or obstruction of the bronchi.

DR. BRAILEY: This man was said to have an "irregular" heart for two years. We may assume that it was fibrillating for at least that long. The heart was really enlarged; he had a Grade II systolic murmur, and an abnormal electrocardiogram. The tracing was not inconsistent with infarction, nor was it inconsistent with left ventricular strain and digitalis effect. Would you agree with that, Dr. Bland?

DR. BLAND: It sounds like an aging heart to me — a nonspecific electrocardiogram, showing the effect of digitalis, I would think.

DR. BRAILEY: What was the nature of the defect? Did he have rheumatic heart disease? Somewhat in favor of that diagnosis is the long-standing fibrillation. But patients with rheumatic heart disease rarely live to seventy-two years of age, and no diastolic rumble was ever described. It does not seem reasonable to consider rheumatic heart disease here.

Did he have hypertensive and arteriosclerotic heart disease? The blood pressure was repeatedly reported as normal. If he had had hypertension in the past of sufficient degree and duration to result in a heart of this size, surely he would have been in severe congestive failure when the blood pressure fell to this level. But the evidence for congestive failure is not very impressive, even two weeks before he came into the hospital. He had marked dyspnea, to be sure, about which we will say more later, but he had no peripheral edema. The liver was not thought to be enlarged, and only transient rales were heard in the chest.

What else might reduce his hypertension other than heart failure? A failure of the adrenal cortex might do so. To be sure, little was said of fatigability, and there were no pigmentary changes recorded. But we wonder a bit about the adrenal glands because we are tantalized by the information that he was exposed to tuberculosis and the serum sodium was remarkably low, perhaps because he was on a low-sodium diet. He had not had it long, however.

Perhaps coronary-artery disease, without a large infarct but with widespread microscopic scarring of the myocardium, was a factor here. The electrocardiogram would not be inconsistent with this possibility. He is said to have had ill described pain, which may have been angina and was probably considered as such since he was given nitroglycerin.

The dyspnea troubled him greatly and certainly troubles me. There are many causes for dyspnea, but if we confine ourselves to those that occur in the chest, they can be roughly divided into pulmonary and cardiovascular. Of the vascular causes, disease on the arterial side of the pulmonary circuit should have resulted in cor pulmonale. He had a tremendous heart, and the right ventricle and right auricle were enlarged. I am not at all sure that he did not have cor pulmonale. He had little evidence of peripheral right-sided heart failure until the last few days of life. Trouble on the venous side of the pulmonary circuit should have resulted in pulmonary edema, of which we have little or no evidence. We are struck by the curious lack of parallelism between his increasing dyspnea and his apparent cardiac performance as reported. It seems certain that he did not have enough cardiac failure per se to account for a vital capacity of 900 cc. and that he must have had some pulmonary disease as well. He undoubtedly had some senile emphysema, but I think this picture presented by his x-ray films is very curious, and I suspect that he had something else — either embolization, with marked widespread fine scarring of the lungs, or an endarteritis.

The evidence for cancer consists of hard nodules, which may have been metastatic supraclavicular lymph nodes, and two gastric washings containing tumor cells. Where shall we put this malignant lesion, which must have been either exfoliating or ulcerating? Is it fair to ask if these cells were epithelial in type?

DR. TRACY B. MALLORY: They were interpreted as that.

DR. BRAILEY: The obvious answer is carcinoma of the stomach, but if we plump for carcinoma of the stomach, we have to make the diagnosis in the face of normal gastric acidity, a not impossible situation but nevertheless rare. The sputum contained no tumor cells on one examination. That does not exclude tumor of the lung. The patient had a productive cough, and it was noted that he swallowed most of his sputum. I do not see why he might not have swallowed the cells for that matter, although we do not usually look for carcinoma of the bronchus by doing gastric washings. Metastatic pilot glands in the neck occur secondary to carcinoma of the stomach, but they are even more commonly found secondary to bronchial disease. It is possible that we shall find no explanation for the low serum sodium. It was probably the result of the low-sodium diet or the edema. But if he did have damage in the adrenal glands by any chance, it is possible that they were

knocked out by metastatic carcinoma — a rather frequent event in carcinoma of the bronchus.

On the whole it seems to me that the odds are in favor of the tumor's being in the stomach, and I have not got the courage to put it anywhere else in the face of positive gastric washings. I have raised a number of questions that I cannot answer intelligently, but since I have to take a stand of some sort I will say that this man had arteriosclerotic heart disease and cor pulmonale, probably on the basis of many small emboli, and carcinoma of the stomach with metastases.

DR. ALFRED KRANES: I wonder if the pulmonary metastases may not have been tumor emboli, and if that was so, I think it is not impossible that carcinoma of the pancreas might produce that picture.

DR. BRAILEY: I should have mentioned that, but tumor emboli occur in carcinoma of the stomach too.

DR. KRANES: But much less commonly, I believe.

DR. BRAILEY: That is right.

DR. BLAND: Does carcinoma of the bronchus frequently metastasize to the supraclavicular lymph nodes?

DR. DONALD S. KING: Quite commonly.

DR. MALLORY: Dr. Warthin, I believe you were interested in this case.

DR. THOMAS WARTHIN: I saw this patient in the Out Patient Department and was struck by the fact that he had heart disease basically. He definitely had abnormal lymph nodes, one of which was characteristic of the Virchow type associated with carcinoma of the stomach. Now seeing the x-ray films, which I had not seen before, I consider them typical of lymphogenous spread of carcinoma of the stomach, such as has been described by Mueller and Sniffen* from this hospital.

DR. BLAND: Would sarcoid cause this picture in the lung?

DR. KING: It could; my opinion is that this was not sarcoid.

CLINICAL DIAGNOSES

Congestive heart failure.
Arteriosclerotic heart disease.
Carcinoma of stomach?
Pulmonary metastases?

DR. BRAILEY'S DIAGNOSES

Cor pulmonale secondary to pulmonary embolization.
Arteriosclerotic heart disease.
Carcinoma of stomach, with metastases.

ANATOMICAL DIAGNOSES

Adenocarcinoma of pancreas, with extension to stomach and metastases to pulmonary lymphatics.

Generalized thrombosis of small pulmonary arteries. Cor pulmonale.

PATHOLOGICAL DISCUSSION

DR. MALLORY: Autopsy showed that this man had a cor pulmonale. The wall of the right ventricle measured 7 mm. in thickness; the left ventricle was normal. The lungs showed diffuse involvement of all the lymphatics with tumor. In a search for the source of the tumor an ulcerated lesion was found in the stomach. A large mass of tumor was found in the region of the pancreas, which at the time of autopsy was interpreted as lymph nodes surrounding the pancreas rather than a primary tumor of the pancreas itself. The subsequent microscopical examination showed that the acinar cells of the pancreas were totally replaced by tumor from end to end of the organ, and I believe that was the primary site. Invasion of the stomach was secondary, but since the secondary tumor had ulcerated into the lumen there is no reason why tumor cells should not be found in the gastric washings. On microscopical examination of the lungs it became evident that nearly all the arteries were surrounded by dilated lymphatics filled with tumor cells and that the majority of them also contained organized thrombi. In only a small number of vessels were tumor cells present within the intra-arterial thrombi, so that tumor embolism was unimportant.

There is no way that I can say from the anatomical findings whether the arterial thromboses, which were old enough to be completely organized, were independent of the carcinoma or secondary to it. I am inclined to think it was secondary, but I cannot prove the point.

DR. KRANES: Did you find thrombosis present in the areas where there was no tumor, or was it so widespread that you could not tell?

DR. MALLORY: The thrombosis was limited to small vessels, and virtually all of them were surrounded by tumor.

DR. BLAND: What we saw in the x-ray films was the lymphatic system of the lungs?

DR. MALLORY: Pulmonary lymphatics in normal conditions are so collapsed that they are scarcely visible. In this lung an artery was surrounded by four or five lymphatics, each so distended with tumor as to be of diameter equal to that of the artery.

CASE 35442

PRESENTATION OF CASE

A forty-six-year-old housewife was seen in the Out Patient Department complaining of pain under the right breast.

She was perfectly well until one month before admission, when after a particularly hard day's work a "catching" pain appeared in the right side of the

*Mueller, H. P., and Sniffen, R. C. Roentgenologic appearance and pathology of intrapulmonary lymphatic spread of metastatic cancer. *Am. J. Roentgenol.* 53:109-123, 1945.

chest, increasing on deep inspiration. The pain persisted for several weeks and then slowly subsided. There was no cough, sputum, hemoptysis, nausea, vomiting or weight loss. Three weeks before admission, while in Canada on a vacation, she consulted a physician. After fluoroscopic examination she was told that she had pleurisy. She received pills for pain and returned home. Since then she was up and around doing housework. During the year before admission she noted a lump in the suprapubic region that swelled intermittently.

At the age of eighteen she had "wet pleurisy" on the right side and was treated at home by a homeopathic physician. Her father and mother were alive and well. Two of nine siblings had died of tuberculosis, but the patient had had no contact with them. An aunt and cousin had died of cancer.

Physical examination showed a well developed, well nourished woman who looked quite healthy. Her lungs were clear to percussion and auscultation. She took deep breaths without apparent difficulty. There was no pain over the ribs. The heart showed a normal sinus rhythm, and no murmurs were heard. Abdominal examination showed no spasm or tenderness. A large, irregular suprapubic mass was present. Pelvic examination confirmed this mass in the posterior cul-de-sac, which extended down to the posterior rim of the cervix. The cervix was not fixed but showed erosions about the external os.

The temperature, pulse and respirations were normal. The blood pressure was 128 systolic, 88 diastolic.

The white-cell count was 7800, and the hemoglobin 12.5 gm. The urine was normal. Cytologic examination of vaginal smears was negative. A chest x-ray film showed scars, a number of which were calcified, in the right upper lobe and to a lesser extent in the left upper lobe. The heart and aorta were not unusual. The nonprotein nitrogen was 19 mg., and the total protein 6.0 gm. per 100 cc.

An operation was performed.

Differential Diagnosis

Dr. Edward Hamlin, Jr.*: How long a period was there between the Out-Patient Department visit and the House admission? It is not clearly stated.

Dr. Benjamin Castleman: A period of one week.

Dr. Hamlin: On receiving this protocol in the mail and after reading it over, I wondered what I was expected to say. It seemed that in all probability some information was being withheld because so little was being presented.

Dr. Castleman: Nothing is supposed to be withheld.

Dr. Hamlin: That is what they always say.

The problem, it seems to me, and I may be wrong, but this is the way I looked at it, is to try to correlate the large suprapubic mass, without any other adjective attached, with the pain in the right chest. I think it is somewhat difficult. Dr. Hanelin, can you help me?

Dr. Joseph Hanelin: I doubt it very much.

Dr. Hamlin: You are my last hope.

Dr. Hanelin: The chest film shows old areas of scarring in both upper lung fields. The left and right costophrenic sulci are clear. There is faint increased density at the right base, which may be due to old pleural thickening.

Dr. Hamlin: Is there any fluid?

Dr. Hanelin: No.

Dr. Hamlin: We have to cling to straws. I do not think there is much value in discussing what a large irregular mass, felt suprapubically and in the posterior cul-de-sac, might be, because as far as I am concerned at the moment it could be anything. There is only one item that, if true, might be of some help (otherwise, fibroids would be far and away the most likely diagnosis): that is the statement made by the patient that the mass "swelled intermittently." It is not carefully stated what relation this had to the uterus.

Dr. Castleman: Do you know, Dr. Sturgis?

Dr. Somers Sturgis: No.

Dr. Hamlin: Therefore, the field is wide open. We can guess about anything we want to. There is nothing outside the realm of possibility. It need not have anything to do with the pelvic organs. Let us look at it from the point of view of trying to correlate the pain in the chest with a mass in the pelvis. We immediately think of Meigs–Cass syndrome.† That, of course, involves ascites and pleural fluid, but neither, apparently, was present here.

The next thing one thinks of is a pulmonary infarct. Infarct could clear up in this period. It is possible that the patient would have had an infarct to account for the pain in the chest, but that does not help a bit.

Dr. Castleman: Excuse me, Dr. Hamlin, I have just found a little more information.

Dr. Hamlin: I thought there would be.

Dr. Castleman: The record states, "On bimanual pelvic examination the lesion seems to incorporate the uterus and movement of the mass is transmitted to the cervix."

Dr. Hamlin: Reward for being overcautious! We then think of metastases. There is no x-ray evidence of metastases. Metastases to lung or pleura, I think, we can ignore for lack of evidence. I want very much to work in perihepatitis. I took occasion to look up perihepatitis in relation to pelvic disease but could not find anything about it, although it certainly was taught when I was a house officer that it was common in association with salpingitis, and we certainly do see many cases accompanied by a perihepatitis. It may simulate gallbladder disease on occasion and produce the typical

*Assistant surgeon, Massachusetts General Hospital.

†Meigs, J. V., and Cass, J. W. Fibroma of ovary with ascites and hydrothorax. *Am. J. Obst. & Gynec.* 33:249-267, 1937.

violin-string type of adhesions. That would be a tempting choice here except that it is extremely hard to envisage a salpingitis as large as this mass apparently was. It is possible certainly, although I have never seen a pelvic mass as large as this due entirely to salpingitis.

We come to the other straw here — namely, a great deal of talk that makes one think of tuberculosis, which is mentioned in the past history and which did not have to be mentioned. Two siblings had tuberculosis, and it would seem that that at least is something we should try to work together. I do not pretend to know very much about pulmonary tuberculosis. The patient certainly had old scarring in the lungs. It would seem to me that if she had tuberculous pleurisy on this occasion, it had cleared up very rapidly. It is possible that she had mild pleurisy associated with it.

How would that fit with the pelvic mass? Tuberculosis of the pelvis is not uncommon in relation to tuberculous salpingitis and endometritis, but again a mass of this size would seem quite unusual. This would be easy if we could put in one or two other diagnoses such as concomitant fibroids.

One thing that occurs to me is a cold abscess. It seems unlikely, but it interests me a good deal. I do not know why I thought of cold abscess in this case. I have not seen one for a long, long time. The fact that this mass varied in size and perhaps the description that Dr. Castleman just gave — the uterus being incorporated in the mass — suggest a large cold abscess filling the cul-de-sac and emerging suprapubically.

I do not like to bet very heavily on any of the possibilities I have mentioned. I am sure there are plenty of others, but since one has to go out on a limb, I may as well make it a long limb and say that this woman had a tuberculous abscess.

DR. CASTLEMAN: Does anyone else want to go out on a longer limb?

DR. STURGIS: Could Dr. Hamlin amplify the statement about intermittent swelling?

DR. HAMLIN: I simply mentioned that in thinking of a cystic mass instead of a solid mass. We have no description to indicate that it was cystic or solid. I carefully did not ask for that because I did not want to hear that it was solid.

DR. STURGIS: Is there any chance of digging out anything from the record in reference to the menstrual cycle? I wonder if endometriosis might come in as a vague possibility.

DR. HAMLIN: It certainly could. I think the fact that any reference to the menstrual cycle was carefully omitted made me ignore that possibility.

DR. CASTLEMAN: I note in the record that the patient stated that the mass seemed to swell and become tender with her menstrual periods.

DR. HAMLIN: I believe you can see the justification for my remarks when I began.

DR. ALLEN G. BRAILEY: Would Dr. Hamlin consider Meigs–Cass disease?

DR. HAMLIN: I did and discarded it because of lack of described ascites.

DR. JACOB LERMAN: Does the fluid in Meigs–Cass syndrome disappear rapidly?

DR. CASTLEMAN: The Meigs–Cass syndrome is a condition in which a fibroma of the ovary is associated with ascites and pleural fluid. Some years ago Drs. Meigs and Cass reported a group of these cases. The pleural fluid does not reaccumulate after the ovarian tumor has been removed; I believe it is resorbed so slowly that, in most cases, it is removed by paracentesis.

CLINICAL DIAGNOSIS

Fibroid uterus.

DR. HAMLIN'S DIAGNOSIS

Tuberculous abscess of pelvis.

ANATOMICAL DIAGNOSES

Tuberculous salpingitis, endometritis, and peritonitis.

Leiomyomas of uterus.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: Dr. Hamlin's limb was pretty good, in spite of all the handicaps, unintentional as they were. The large mass that was felt was the ordinary leiomyomatous uterus, but associated with it, on the serosal surface of the uterus, as well as on the tubes, ovaries and peritoneum, were very small, grayish nodules. At the time of operation the surgeon thought they might possibly be carcinomatous. Our microscopical sections proved that they were all tuberculous and that this patient had tuberculous salpingitis, endometritis and peritonitis, the peritonitis being present all over the pelvic cavity as well as on the surface of the appendix. It is quite possible, although it was not explored, that she had a perihepatitis as a result of salpingitis. The surgeon removed the uterus and both tubes but left the ovaries. The tuberculosis appeared quite active, and I imagine that the patient has been sent to a sanatorium.

The New England
Journal of Medicine

Formerly
The Boston Medical and Surgical Journal
Established 1828

Official Organ of
The Massachusetts Medical Society
and
The New Hampshire Medical Society
Owned by the Massachusetts Medical Society and Published Weekly under the Jurisdiction of the Committee on Publications

Richard M. Smith, M.D., *Chairman*
James P. O'Hare, M.D. Conrad Wesselhoeft, M.D.
Oliver Cope, M.D. John Fallon, M.D.

Joseph Garland, M.D., Editor

Associate Editors
Thomas H. Lanman, M.D. Donald Munro, M.D.
Henry Jackson, Jr., M.D.

Clara D. Davies, Executive Editor
Robert O'Leary, Assistant Editor

Editorial Board
C. Guy Lane, M.D. Maxwell Finland, M.D.
Henry R. Viets, M.D. Carroll B. Larson, M.D.
Robert M. Green, M.D. C. Stuart Welch, M.D.
Dwight O'Hara, M.D. Vernon P. Williams, M.D.
Fletcher H. Colby, M.D. Benjamin Castleman, M.D.
Robert L. Goodale, M.D. Hugh R. Leavell, M.D.
Chester M. Jones, M.D. J. Englebert Dunphy, M.D.
Harvey R. Morrison, M.D. Charles H. Burnett, M.D.

Subscription Terms: $7.00 per year in advance, postage paid, for the United States (medical students, $4.00 per year); Canada, $8.00 per year (Boston funds); $9.50 per year for all foreign countries belonging to the Postal Union.

Material should be received not later than noon on Thursday, three weeks before date of publication.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

THE CONTINUING CHALLENGE OF PULMONARY EMBOLISM

After World War I it was noted that postoperative pulmonary embolism was on the increase. To be sure, some of this was only apparent because of the better recognition of the condition both clinically and post mortem. An actual increase was, however, accepted and was variously ascribed to exhaustion and poor health resulting from the war, to the increasing age of patients subjected to surgery, and to the bolder operative procedures that improvement in anesthesia and surgical technics made possible in patients who would previously have been considered poor risks. It is quite probable that the last two factors as well as better recognition of the condition by internist, surgeon and pathologist alike accounted for the increasing awareness of this threat. The same reasons may still apply today, as well as others not yet defined favoring an increased amount of thromboembolic disease.

As time went on it also became obvious that pulmonary embolism was much more common in medical patients than had been thought; this important complication had been previously in many cases called something else, in particular hypostatic pneumonia or pulmonary edema due to heart failure.

Thus, it was only natural that during the last decade vigorous action should have been taken to try to prevent pulmonary embolism, which was often fatal after serious surgical operations and which was also one of the commonest causes of death in cases of chronic cardiac disease. Various measures were introduced to curb the threat. Two of the simplest and perhaps the best have been early mobilization after surgery and the use of penicillin to help to make such mobilization possible. Stasis favoring thrombosis in the leg veins, the commonest cause of pulmonary embolism, was thus minimized. Also, efforts were made to reduce pressures and positions causing stasis during surgical operations themselves and to ease the strain of bowel movements, to reduce "bedpan death."

Two special measures, which were widely introduced to limit the hazard of pulmonary embolism and which have had their vigorous proponents, have been the use of anticoagulants and ligation of the femoral veins, both as prophylaxis and as treatment. Statistics have been presented to indicate the value of both methods in a more or less parallel fashion, and many individual cases have been known and some reported in which the institution of either or both of these therapies has apparently been life saving. But there have been failures, too, often not so distinctly delineated.

In the present issue of the *Journal* an interesting and important experience of the Department of Pathology of the Massachusetts General Hospital is presented. Despite the institution of the measures cited above during the five-year period from 1943 to 1947 inclusive, there was a definite increase in the notation of fatal pulmonary embolism found at autopsy over that in two previous five-year periods, 1931 to 1935 inclusive, and 1936 to 1940 inclusive (4.42 per cent of 2083 autopsies in 1943

to 1947 as compared to 2.16 per cent of 1991 in 1931 to 1935 and 3.66 per cent of 1832 in 1936 to 1940). This finding is, at first thought, discouraging and even appalling, and most certainly presents a continuing challenge, but there are certain features whose consideration is necessary before final conclusions are drawn.

In the first place the actual incidence of unquestioned fatal pulmonary embolism in patients whose femoral veins were bilaterally ligated either prophylactically (4) or therapeutically (6) was only 0.5 per cent (10 patients out of 1929 cases so treated). There was another group of 11 cases with smaller emboli after the ligation, making a total of 21, or 1.1 per cent. Four other patients had their veins ligated *after* embolism that subsequently proved to be fatal. One other had an embolus consisting of a renal-cell carcinoma. This leaves a balance of 63 cases with fatal pulmonary embolism, 14 with large, possibly fatal embolism, and 105 with small emboli who did not have leg-vein ligation, a total of 182 as compared with 21 who did have the ligation. One would, of course, like to know how many patients there were who were comparably ill or operated upon (not just total admissions) of whom these 182 made a part. It is quite possible that the ratio of pulmonary embolism might be found to be higher in that group than in those subjected to ligation, as data already published from the Massachusetts General Hospital have indicated.[1-3] This analysis, though difficult, would be well worth while in amplifying the data already presented. Incidentally, it is of much interest and doubtless of considerable importance to note the fact that, on the average, the patients admitted to the hospital in the last five-year period — that is, from 1943 to 1947 inclusive — were eight years older than those admitted in the first period, 1931 to 1935 inclusive. In addition, it has been stated that a diminished mortality from shock, infection and pneumonia in recent years has put thromboembolic disease more in the limelight.

However, even if ligation and anticoagulant therapy (800 cases received Dicumarol at the Massachusetts General Hospital during 1947 alone but were not analyzed in this report) reduce the threat of pulmonary embolism, as has been the experience of most surgeons and internists, they are not yet good enough since death can occur despite them, as clearly shown by the paper of Roe and Goldthwait in the individual case reports, several of which revealed thrombi in the veins proximal to (that is, nearer the heart than) the ligation site. Moreover, these measures have not, in all probability, been applied to enough cases or always in adequate degree to obtain the best results. Finally, the high percentage of unanticipated, fatal pulmonary embolism in this series is rather surprising especially in a hospital where the staff has presumably been on the alert; this fact simply indicates the need of still more attention to this frequent complication both postoperatively and in medical patients.

Thus, the challenge of pulmonary embolism still exists in major form.

References

1. Allen, A. W., and Donaldson, G. A. Venous thrombosis and pulmonary embolism. *Bull. New York Acad. Med.* **24**:619-635, 1948.
2. Colby, F. H. Prevention of fatal pulmonary emboli after prostatectomy. *J. Urol.* **59**:920-924, 1948.
3. Carlotti, J., Hardy, I. B., Jr., Linton, R. R., and White, P. D. Pulmonary embolism in medical patients: comparison of incidence, diagnosis and effect of treatment in two hundred and seventy-three cases at Massachusetts General Hospital in two five year periods (1936 to 1940 and 1941 to 1945 inclusive). *J. A. M. A.* **134**:1447-1452, 1947.

FURTHER PSEUDODOXIA

THE "total health of the child" is a popular present-day concept, which hardly any physician contemplates without comprehension of the importance of child happiness and the security of his family relations. It is well that this should be so. However, this relatively new recognition of the importance of mental hygiene is likely to uncover practices that although dimly recognized as unsatisfactory, have not hitherto seemed enough of a menace to health to warrant serious attention. Some of these practices were mentioned by Bakwin[1] in 1945 as "pseudodoxia pediatrica," and among them is also the pseudoauthoritative writing that is found in some of the semiofficial and voluntary journals upon the subject of posture. A review of the literature of the last seven years reveals some strictly scientific articles on the posture of the child, among which should be mentioned, "New Approach to Quantitative Analysis of Children's Posture" by Robinow, Leonard and Anderson.[2] This, with its many illustrations, has a highly instructive value and is

notable also for restraint and factual basis. For its content of good sense, though not comparable to the first as a product of research, "Changing Concepts in Posture Training," by L. W. Irwin[3] should also be mentioned.

But the collection of the last seven years includes much that must be discarded by the critical reader. Some of this material in the hands of unprotected parents seems almost certain to lead to improper care of children, and it is regrettable that it should receive the prestige of publication. These pages contain dogmatic instructions concerning the baby's standing and sitting habits, and especially his sleeping posture, which must be followed or deformity is said to result. It is indeed surprising that no attempt has yet been made to correct the posture of the fetus in utero. This somewhat cloistered stage of development certainly defies all the rules of the posturites, and for a time that seems long enough to lead to a permanent deformity if a cramped position for a sustained period can deform. There is room for doubt that even if a baby insists upon sleeping on his chin, to mention one practice strongly decried by these writers, such a position necessarily leads to deformity. A more important basis for fear is the menace to mother-child relations of constant nagging correction of such a habit in baby or child.

In appraising the posture of the school child it is apparent to many that unlovely slouches or slumps are more apt to be the result than the cause of ill health. It is apparent also that spontaneous correction occurs in the vast majority of school children when no true structural deformity exists. In view of this spontaneous tendency to correction, one is led to doubt the value of special corrective exercises as provided by some schools, especially if they include separation into special classes. The possibility exists that special classes themselves may lead to social maladjustment.

References

1. Bakwin, H. *Pseudodoxia pediatrica. New Eng. J. Med.* **232**:691-697, 1945.
2. Robinow, M., Leonard, V. L., and Anderson, M. New approach to quantitative analysis of children's posture. *J. Pediat.* **22**:655-663, 1943.
3. Irwin, L. W. Changing concepts in posture training. *J. Health & Phys. Educ.* **17**:522-524 and 573, 1946.

CHEST X-RAY PROGRAM — A REPORT OF PROGRESS

The Boston Chest X-Ray Program, as of October 14, reported that 139,442 x-ray films had been taken, of which 99,939 had been processed. This encouraging beginning has been made in only eighteen operating days.

An analysis of the practically 100,000 processed films shows that 95.63 per cent were negative and 1891, or 1.89 per cent, gave some evidence of disease. Definite tuberculosis was evident in 826 cases and suspected tuberculosis in 489. Nontuberculous chest disease appeared on 360 films, and cardiovascular disease on 216.

The Committee on Nontuberculous Chest Disease, a subcommittee of the Medical Committee of the Program, is naturally concerned about the treatment and disposal of patients in whom chest disease of a nontuberculous nature is found, and has suggested procedures pertaining to their care.

These recommendations point out that cancer is the most important diagnosis to be considered in the evaluation of nontuberculous pulmonary disease, and emphasize the criteria necessary for its identification, as well as the necessity for rapid processing of films in order to facilitate early diagnosis. Particularly stressed are the definition of those lesions that should cause the patient to be designated as a cancer suspect, and the further management of such cases.

Suitable orientation of physicians in this regard is important in that all cases of nontuberculous pulmonary disease discovered will be referred back to the family doctor or to the Massachusetts Medical Society for advice if there is no family physician, but private care is desired. Other patients will be referred to established thoracic clinics in or near Boston.

One of the most persistently discouraging facts about cancer of the lung, as demonstrated by Overholt and Schmidt,* is the long interval of ten months that elapses, on the average, between the patient's first visit to the doctor and the time when the diagnosis is made. The lessons to be learned from the Boston Chest X-Ray Program should be of value in cutting down this "tragic interlude."

*Overholt, R. H., and Schmidt, I. C. Survival in primary carcinoma of lung. *New Eng. J. Med.* **240**:491-497, 1949.

TALE OF TWO CITIES

OLD ways are best in Budapest, according to observations recently published by Suranyi.* The infant mortality in the twin cities had reached the deplorable level of 269 per 1000 in July and August of 1945; in the corresponding months of 1948 it had dropped to 57. The reason given for the improvement was a health campaign in which breast feeding was emphasized, aided in a practical manner by the application of short-wave therapy to the breasts. Ten such treatments, it is said, resulted in a prolonged 50 per cent increase in milk excretion in a third of the cases.

Figures indicate that up to 4,166,500 gm. of human milk have been collected and dispensed in one month through the 19 centers that have been established in the city. An average of 2500 infants per month have received the benefits of this service, preference being given to premature and sick babies. During a test period the mortality rate among infants receiving the breast milk was 36 per 1000, as against a rate for the city as a whole of 79 per 1000.

Like Horace's Spartans, the women of Hungary seem to have opposed to the strokes of adversity their gallant breasts.

*Suranyi, G. I problemi dell' alimentazione del lattante e la loro soluzione a Budapest. *Il Lattante* **20**:129-139, 1949.

AMERICAN ACADEMY OF PEDIATRICS

THE annual meeting of the American Academy of Pediatrics, which will be held at the Palace Hotel in San Francisco from November 12 to 17, promises to be of great interest to all pediatricians, as well as the many general practitioners whose practice includes pediatric cases. The program consists of seminars, original papers and round-table and panel discussions on the various pathologic conditions and infections encountered in infancy and childhood; attention will also be given to mental, emotional and endocrine problems.

This congress marks the eighteenth annual convocation of the Academy. The publication of the results of the surveys on child health services in various states[1, 2] lends added significance to the meeting of the organization primarily responsible for this investigation. The *Journal* wishes the Academy every success in the various surveys and in the continued efforts to solve the problems of child health in the United States.

REFERENCES

1. Editorial. "Pattern for child health." *New Eng. J. Med.* 238:[illegible] 1948.
2. Baty, J. M., and Snedeker, L. Child health services in Massachusetts. *New Eng. J. Med.* **241**:454-461, 1949.

A hundred years hence, some philanthropist... will probably deplore . . . the gullibility of civilized man in whatever pertains to his individual health. While the elements of humanity remain as they are, there will be no lack of cheats and impostors; and the pleasure of being cheated will continue to be as great as when Butler wrote his Hudibras.

Boston M. & S. J., *October 31, 1849*

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

GARDNER — Edwin D. Gardner, M.D., of Marion, died on October 12. He was in his sixty-fifth year.

Dr. Gardner received his degree from Harvard Medical School in 1910. He was former chief of surgery at St. Luke's Hospital, and was chief of the surgical staff of Tobey Hospital, Wareham. He was a member of the American Urological Association and a fellow of the American College of Surgeons and American Medical Association.

His widow and two sisters survive.

HATT — Rafe Nelson Hatt, M.D., of Honolulu, Hawaii, died on May 27. He was in his sixtieth year.

Dr. Hatt received his degree from Tufts College Medical School in 1918. He was formerly chief surgeon at the Shriners Hospital for Crippled Children, Springfield, and consulting orthopedic surgeon at Springfield and Wesson Memorial hospitals. He was a past president of the Springfield Academy of Medicine and was a nonresident member of the Massachusetts Medical Society. He was a member of the American Orthopaedic Association and the American Academy of Orthopaedic Surgeons and a fellow of the American College of Surgeons.

His widow, a son, two daughters and a granddaughter survive.

WATTERS — William H. Watters, M.D., of Boston, died on October 11. He was in his seventy-fourth year.

Dr. Watters received his degree from Boston University School of Medicine in 1900. He was professor emeritus of preventive medicine at Boston University School of Medicine and was a member of the American College of Physicians and a fellow of the American Medical Association.

His widow survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

CHANGES IN ACT FURTHER PROVIDING FOR THE CARE OF CERTAIN INFANTS

Changes in the law relating to the care of premature infants enacted by the General Court (Chapter 601, Acts of 1949) became effective on October 25, 1949. The responsibilities for the care of premature infants formerly allocated to local boards of welfare are now transferred to local boards of health. This transfer is made because this is primarily a matter pertaining to health and also because of the hope that it will remove the welfare stigma that has interfered with the full use of legal provisions in the past. Many families who could afford to pay for hospitalization of ordinary length find it impossible to meet the cost of the prolonged periods sometimes necessary for premature infants. It is the purpose of this legislation to help such cases.

The changes in Chapter 601 are outlined as follows:

Administration

Local boards of health or local health jurisdictions, rather than local boards of welfare, are now responsible for the administration of this law.

Weight

Defined at 5½ pounds or less at birth, instead of 5 pounds or less, to conform to federal and other state definitions.

Reporting of Premature Births

By hospital — to the local board of health or local health jurisdiction of the town where the mother resides instead of the local board of welfare of the town where the infant is born.

By physicians (for premature births outside hospitals) — to the local board of health or local health jurisdiction of the town where the infant is born instead of to both boards of health and welfare.

Payment for Hospitalization

Only for infants weighing 4½ pounds or less at birth (if parents are unable to pay).

By local health agency — by local board of health or local health jurisdiction instead of by local board of welfare of the town of mother's residence. If the mother's settlement is in another town the board of health of the town of settlement will reimburse the board of health of the town of residence on written notification within sixty days.

No expense shall be reimbursed that was incurred more than ten days (instead of five) prior to receipt of original notice sent to local board of health.

Ceiling rates for hospitalization are established by the Massachusetts Department of Public Health.

By Massachusetts Department of Public Health — for cases with no legal settlement, hospitalization will be paid by the Massachusetts Department of Public Health.

Copies of the Act are being sent to all physicians, hospitals, boards of health, boards of welfare, public-health nursing organizations and others interested.

Attention is called to the importance of acquainting parents who may need financial assistance with the provisions of this act.

CORRESPONDENCE

ON THE HEATING OF INFANT FORMULAS

To the Editor: In the article by Drs. Joseph C. Merriam and C. G. Tedeschi, which appeared in the August 25 issue of the *Journal*, the results of terminal heating of infant formulas under steam pressure were discussed. The conclusion was reached that, although terminal heating at 15 pounds of pressure for five minutes or at 6 pounds for ten minutes produces bacteriologically safe products, there are some undesirable side effects in the form of coagulum in the formula and sticking of the nipple shields to the nipples. Reference is made to the New York State Sanitary Code, Chapter II, Regulation 35, as the source of these recommended procedures.

The terminal heating requirements of Regulation 35 are based on the experience of Cummings in the Michigan State Health Department, on the recommendations of the subcommittee of the American Hospital Association, which made a study of terminal heating of formulas, on extensive studies made in the New York State Department of Health and on suggestions submitted by hospitals in New York State at the time Regulation 35 was in preparation. Two of the three methods have been adopted by the American Academy of Pediatrics.

There is a wide experience in the use of all three methods of terminal heating. The success that one hospital has with a given method may not be duplicated in another hospital. This may be attributable to differences in formula, to differences in the heating efficiency of the equipment in use and to the human factors of careless timing and failure to remove the formula from the autoclave as soon as possible. Small bottles filled too full often result in nipple plugging. In general, the Department of Health personnel are in favor of lower temperatures for terminal heating of formulas. The requirement of 250° for five minutes was included in the regulation as a permissive provision at the request of certain hospitals that were using this method prior to the adoption of Regulation 35. In view of the fact that autoclaves can be equipped with an attachment that will make it possible to operate them at any one of the three temperatures allowable under Regulation 35, this regulation is applicable in any hospital. It is recommended that hospitals experiment with a few formulas in adequate size bottles, until they find the method that seems best suited to their personnel and their types of formula. Since all hospitals in New York State are now carrying out terminal heating of formulas and many of them are using steam pressure, the formation of coagulum and the sticking of nipple shields to nipples do not seem to constitute a universal problem.

The bacteriologic results mentioned by Drs. Merriam and Tedeschi are parallel to those obtained in the New York State Department of Health and by others who have studied this problem.

These few comments have been submitted in an effort to clarify any misunderstanding that might arise concerning the practicability of the requirements of the New York State Sanitary Code for the terminal heating of infant formulas.

RAY E. TRUSSELL, M.D.
Professor of Preventive Medicine

Albany Medical College
Albany, New York

BOOK RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

George R. Minot Symposium on Hematology. By William Dameshek, M.D., and F. H. L. Taylor, Ph.D., editors. 4°, cloth, 984 pp., with illustrations and tables. New York: Grune and Stratton, 1949. $12.00.

This honorary volume was issued in commemoration of the sixtieth birthday of Dr. George R. Minot in 1945. One hundred and fifty-five colleagues and friends of Dr. Minot contributed eighty-three articles on the blood and related

subjects. The articles were originally published in *Blood* during 1948 and 1949, and are here brought together in one volume as a "Festschrift" through the generous financial support of the Lederle Laboratories and Mr. J. K. Lilly. The text is preceded by a full-page portrait of Dr. Minot and by his biographic data. The first article is a reprint from the *Journal of the American Medical Association* of August 14, 1926. This article, "Treatment of Pernicious Anemia by a Special Diet," which was by Dr. Minot and Dr. William P. Murphy, represented the outstanding contribution of these two physicians and won them the Nobel prize. The text is divided into seven parts into which the various articles are classified: pernicious anemia; hemolytic anemia; anemia other than pernicious or hemolytic; blood-clotting phenomena and hemorrhagic disease; leukemia; biologic and cytologic reactions of blood and blood-forming tissues, subdivided into red cells, white cells, blood-forming organs and certain biochemical aspects; and general practice, containing two contributions on peptic ulcer and on diabetic coma. There are indexes of authors and subjects.

The original article of Minot and Murphy has long been out of print and is made available in this volume. The book is recommended to all medical libraries.

NOTICES

ANNOUNCEMENTS

Dr. Robert J. Fahey announces the opening of offices for the practice of internal medicine at 119 High Street, Medford, and 520 Commonwealth Avenue, Boston.

Dr. A. William Reggio announces the change of his address from 2301 Connecticut Avenue, N.W., Washington, D. C., to School Street, Medfield, Massachusetts.

SOUTH END MEDICAL CLUB

A luncheon meeting of the South End Medical Club will be held at the headquarters of the Boston Tuberculosis Association, 554 Columbus Avenue, Boston, on Tuesday, November 15, at 12 noon. The speaker will be Dr. Hans Waine, medical director of the New England Chapter of The Arthritis and Rheumatism Foundation, who will discuss arthritis and rheumatism, and especially Cortisone, the new treatment for these diseases.

Physicians are cordially invited to attend.

GREATER BOSTON ASSOCIATION OF MEDICAL TECHNOLOGISTS

A meeting of the Greater Boston Association of Medical Technologists will be held at the Nurses Home of the New England Baptist Hospital, on Tuesday, November 8, at 7:30 p.m. Dr. Donald A. Nickerson will speak on the subject "Evaluation of Blood Sugar Technics."

NEW ENGLAND CARDIOVASCULAR SOCIETY

The following scientific program of the New Engla Cardiovascular Society for 1949–1950 has been announce (all meetings will be held on Monday evenings at 8:15):

November 7. Massachusetts General Hospital. Edward Bland, M.D., chairman.

December 5. Peter Bent Brigham Hospital, Samuel A. Levine, M.D., chairman.

January 9. Boston City Hospital. Laurence B. Ellis, M.D. chairman.

February 6. Massachusetts Memorial Hospitals. Rober W. Wilkins, M.D., chairman.

March 6. Beth Israel Hospital. Herrman Blumgart, M.D. chairman.

April 3. Children's Medical Center (House of the Good Samaritan and Children's Hospital). Benedict F. Massell, M.D., chairman.

May 8. Annual meeting.

Members who wish to give papers and are staff members of hospitals in which no meeting has been scheduled are requested to submit papers to the Secretary (Dr. Benedict F. Massell). If sufficient papers are submitted, an additional meeting will be arranged.

SOCIETY MEETINGS AND CONFERENCES

OCTOBER 3–MAY 19. Massachusetts Department of Mental Health. Postgraduate Seminar in Neurology and Psychiatry. Page 286, issue of August 18.

NOVEMBER 6 AND 7. American Society for the Study of Arteriosclerosis. Page 594, issue of October 13.

NOVEMBER 7. New England Cardiovascular Society. Page 678, issue of October 27.

NOVEMBER 7–9. National Society for Crippled Children and Adults. Page 184, issue of July 28.

NOVEMBER 7–12. International College of Surgeons. Page 251, issue of August 11.

NOVEMBER 8. New England Society of Anesthesiologists. Page 630, issue of October 20.

NOVEMBER 8. Edward K. Dunham Lecture. Page 678, issue of October 27.

NOVEMBER 8. Greater Boston Association of Medical Technologists. Notice above.

NOVEMBER 8–10. Salmon Memorial Lectures. Page 594, issue of October 13.

NOVEMBER 10. Human Streptococcicosis. Dr. Louis Weinstein. Pentucket Association of Physicians. 8:30 p.m. Haverhill.

NOVEMBER 10. Edward K. Dunham Lecture. Page 678, issue of October 27.

NOVEMBER 14–17. American Academy of Pediatrics. Page 251, issue of August 11.

NOVEMBER 15. South End Medical Club. Notice above.

NOVEMBER 16. Massachusetts State Society of Examining Physicians. Page 324, issue of August 25.

NOVEMBER 23. Pediatric Seminar for Physicians and General Practitioners. Page 550, issue of October 6.

(*Notices concluded on page xiii*)

Take a leaf from the book of Doc Wise
Whom his patients all praise to the skies:
He reads every ad
In the* Journal, *begad
And knows all the wherefores and whys.

5